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CONTENTS

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IN THIS ISSUE

THE great and growing interest in mental disorders, especially in their prevention, has stimulated much epidemiological research designed to obtain evidence on the causes of different kinds of mental disorders which can be the basis for developing preventive programs. Aware of this interest and of the many recent studies which have evaluated data on associations between a variety of factors and mental disorder, in 1959 the Milbank Memorial Fund sponsored a Round Table meeting at Arden House, at which present knowledge about causation of mental disorder was discussed. In preparation for this meeting, eight distinguished authorities were asked to prepare review articles summarizing the evidence relating to different kinds of causes which had been thought to lead to mental disorders. The papers were distributed to the participants in advance of the meeting. At the meeting, the discussion of each review paper was opened by a previously designated participant; a general discussion followed; and the reviewer then added his own comments on the discusion.

In this and the following two issues of the *Quarterly* seven of the review papers, the opening discussion and a summary of the general discussion will be published. The first paper on "Genetical Etiology in Mental Illness" by Professor Jan A. Böök, was published in July, 1960. Unfortunately, the discussion of this paper was not published in the *Quarterly,* but it will be included in a volume of collected papers from the meeting which will be made available later in 1961, under the general title of CAUSES OF MENTAL DISORDERS: A REVIEW OF EPIDEMIOLOGICAL KNOWLEDGE, 1959.

This issue of the *Quarterly* includes an introductory statement outlining the objectives of the meeting, a brief abstract of each review article and a list of the participants.

Two of the review papers, one by Professor Brian MacMahon on "Physical Damage to the Fetus" and one by Dr. George James on "The Epidemiology of Mental Disorder Associated with Damage to the Brain after Birth" appear in this issue.

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Cross tabulations of regular census data by state of birth and state of residence make it possible to differentiate populations on the basis of whether they have moved from one state to another. Since 1940 each census has included a question on specific place of residence one or five years previous to the census. Here again the classifications yield information as to whether a given type of move occurred during the period considered. Occasionally private studies or sources have yielded limited data on number of moves and residence history since marriage. In a paper "Duration-of-Residence Analysis of Internal Migration in the United States," Dr. Karl E. Taeuber discusses the migration information provided by a question on duration of residence, and presents the first national migration data derived from this approach. The data are from the National Lung Cancer Mortality Study with which the author is affiliated.

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It is only during a relatively short "fertile period," approximately in the middle of woman's menstrual cycle, that there is appreciable chance of conception. Research into the survivorship of sperm and ova within the female have indicated that the average length of the fertile period is almost certainly less than three days and probably less than two days. In an article "Length of Fertile Period" Dr. Robert G. Potter assembles three additional lines of evidence which collectively suggest that the fertile period is typically less than 48 hours. One includes Dr. Christopher Tietze's estimates made on the basis of data and given assumptions regarding frequency of intercourse and conception delays. The other two are Potter's and they are derived by adapting Tietze's method to data on artificial insemination by donor and to speed of conception among women

reporting different coital frequencies. More precise knowledge of the length of the fertile period would be beneficial to various fields such as the treatment of sterility, the more effective use of the rhythm method of contraception, and artificial insemination.

Participants

Jan A. Böök, M.D., *Professor and Director, The State Institute for Medical Genetics, University of Uppsala, Sweden*

Frank G. Boudreau, M.D., *President, Milbank Memorial Fund*

G. Morris Carstairs, M.D., *Director, Medical Research Council Unit for Research on the Epidemiology of Psychiatric Illness, London*

John H. Cumming, M.D., *Director, Mental Health Research Unit, New York State Department of Mental Hygiene, Syracuse*

Paul M. Densen, D.Sc., *Deputy Commissioner of Health, The City of New York*

H. Warren Dunham, Ph.D., *Professor of Sociology and Anthropology, Wayne University; and, Director, Epidemiological Studies, Lafayette Clinic, Detroit*

Ernest M. Gruenberg, M.D., *Milbank Memorial Fund*

E. Gartly Jaco, Ph.D., *Director of Socio-Environmental Research, Cleveland Psychiatric Institute and Hospital; and, Associate Professor, Departments of Sociology and Psychiatry, Western Reserve University*

George James, M.D., *First Deputy Commissioner of Health, The City of New York*

Morton Kramer, D.Sc., *Chief, Biometrics Branch, National Institute of Mental Health, Bethesda*

Alexander H. Leighton, M.D., *Professor of Sociology and Anthropology, Cornell University; and, Professor of Psychiatry (Soc. Psych.), Cornell University Medical College*

Paul V. Lemkau, M.D., *Professor of Public Health Administration, The Johns Hopkins University School of Hygiene and Public Health*

Brian MacMahon, M.D., *Professor and Head, Department of Epidemiology, Harvard University School of Public Health*

H. B. M. Murphy, M.D., *Section of Transcultural Psychiatry, Allan Memorial Institute, McGill University, Montreal*

Benjamin Pasamanick, M.D., *Professor of Psychiatry, Ohio State University College of Medicine; and, Director, Research Division, Ohio State Department of Mental Hygiene and Correction, Columbus*

Donald D. Reid, M.D., *Professor of Epidemiology, London School of Hygiene and Tropical Medicine*

George Rosen, M.D., *Professor of Health Education, Columbia University School of Public Health and Administrative Medicine*

Staff

Miss Dorothy G. Wiehl

Matthew Huxley Richard V. Kasius

THE CONFERENCE ON CAUSES OF MENTAL DISORDERS: A REVIEW OF EPIDEMIOLOGICAL KNOWLEDGE, 1959

ERNEST M. GRUENBERG, M.D., AND MATTHEW HUXLEY

WITHIN the past two decades there has been such a marked growth of interest in developing methods for preventing and treating mental disorders that the financial resources supporting relevant research have, at times, outstripped the capacity of the professions to provide properly qualified investigators. For it is extremely difficult for anyone to get a clear perspective on the kinds of actions which might profitably be taken in the attack upon mental illness. To arrive at this perspective requires the ability to sift the large bodies of a very varied literature in order to pick out the few examples of well-planned investigations. This ability, in turn requires a scientificaily developed understanding of the phenomena of mental illness and the knowledge to distinguish the phenomena from the plethora of theoretical formulations and speculations about the mysteries these illnesses represent.

The ability to develop effective preventive work in the mental disorders can only stem from the process of clarifying these mysteries. Over a hundred years ago this same process was developed by the forerunners of today's public health professionals to investigate the nature of the then mysterious afflictions which attacked men's physical bodies. The process of clarification has become today's science of epidemiology, the basic tool of preventive medicine whether it be directed to men's minds or men's bodies.

As the reader of this book will soon become aware, many pieces of evidence have been, and are being, gathered by many different kinds of professional people: statisticians and physicians, administrators and psychiatrists, sociologists and psychologists, and even professional epidemiologists. However,

regardless of who gathers the data, and regardless of who is drawing the conclusions, and regardless of what any particular investigator calls this "clarification of mysteries," conclusions concerning the physical, psychological or social forces affecting the occurrence of a particular mental disorder are epidemiological conclusions.

In 1959, the Milbank Memorial Fund, conscious of the rapid growth in professional interest and of the volume of new data that had appeared in the last ten years, asked eight distinguished authorities to prepare review articles summarizing the present state of knowledge about different kinds of causes which had been thought to lead to mental disorders. These eight papers form a convenient classification. This convenience cannot, and should not, hide the fact that each of these divisions interacts and impinges upon the others. Nevertheless the convenience of a classification which tends to correspond to areas of competence amongst today's professions, and the consequent ability to have prepared systematic, critical, careful reviews of the available evidence regarding the relationship between postulated cause and particular disorder, far outweighs the disadvantages.

The papers were circulated to sixteen participants at a two-day meeting where they were discussed, having been read previously by the participants. At the meeting, each paper was initially reviewed by a discussant, whose remarks opened an hour-long general exchange of ideas on the topic under consideration. These opening remarks together with a summary of the general discussion which ensued, will be found following each paper and will give the reader an opportunity to see the response of 16 experts to the stimuli of the review papers.

The methodology of conducting investigations was not discussed although some critical evaluations of the suitability of certain methods were.[1]

[1] Those interested in such matters are referred to the following items:
Reid, D. D.: Epidemiological Methods in the Study of Mental Disorders. Public Health Papers No. 2. Geneva: World Health Organization 1960. 70 pp.

(Continued on page 9)

These papers provide a stock-taking of our present state of knowledge regarding the epidemiological evidence about the causes of mental disorders.

The viewpoint implicit behind the discussions reported here is that the application of scientific methods to the problems of mental disorder will lead us to the development of effective preventive methods. No particular theory or viewpoint about the nature of mental disorders or their causes is expounded here. What will be found is a critical appraisal of established knowledge regarding the distribution of mental disorders in populations. To these appraisals are added ideas on the research needed to settle those outstanding issues which suggest that various physical, social, or psychological factors are of great importance in the production of particular disorders. No proposals, however, will be found which attempt to translate these appraisals into action programs to affect the amount of mental disorder occurring at the present time.

Finally, the bibliographies appended at the end of each chapter are selective of the most important data relevant to the review paper in question and are not to be considered as exhaustive.

The Milbank Memorial Fund would like to use this opportunity to express its deep appreciation to the participants at this Round Table meeting and particularly to the authors of the review papers who put into their preparation all of the accumulated experience and all of the knowledge and judgment

Some general discussion on methodology will be found in:

"Report of World Health Organization Study Group on Schizophrenia—Geneva, September 9–14, 1957." *American Journal of Psychiatry,* 115, 865–872 (April, 1959).

Discussion of current investigations and issues which investigators would wish to see examined further are reported in:

COMPARATIVE EPIDEMIOLOGY OF THE MENTAL DISORDERS. Proceedings of the 49th Annual Meeting of the American Psychopathological Association, New York City, February, 1959. (Eds.: Paul H. Hoch and J. Zubin). New York: Grune and Stratton (in press).

FIELD STUDIES IN THE EPIDEMIOLOGY OF MENTAL DISORDERS. Proceedings of the Work Conference on Problems in Field Studies in the Mental Disorders [held in New York City] February 16–19, 1960, under the auspices of the American Psychopathological Association (Ed.: J. Zubin). New York: Grune and Stratton (in press).

of their very full lives as to where we stand in understanding the processes which lead to mental disorder.

I. *Jan A. Böök, M.D.: Genetical Etiology in Mental Illness.*

This examination of the existing evidence for genetic factors in mental illness is concerned with three areas: First, an analysis of the relationship between specific genes and specific disorders emphasizing the concept of "inborn errors of metabolism" as exemplified by phenylketonuria. Second, a detailed review of the evidence of genetic factors in schizophrenia which concludes that major gene differences do exist, but that they must be viewed as leading to a capacity for the disorder with other, and as yet unknown, factors postulated as operating at the same time as the genetic factor. The role of genes in the manic-depressive parallels that of genes in schizophrenia; and it appears clear that there must be significant biological differences between the two syndromes since schizophrenia does not occur with an increased frequency among relatives of manic-depressives and vice versa. Finally, Dr. Böök concludes that progress in the area of medical genetics can only be expected through studies of conditions which are closely linked to specific gene disturbances using a diagnostic method that identifies an almost one-to-one relationship with the causative mutant gene. Present diagnostic criteria in the most prevalent and important mental disorders are inadequate for genetic studies because they do not define and delimit the disease entity clearly.

II. *Brian MacMahon, M.D.: Physical Damage to the Fetus.*

A detailed review of the available evidence linking the occurrence of mental disorders of various types with the action of a wide range of specific agents acting during fetal development (infections, radiation energy, jaundice, asphyxia, nutritional deficiencies), is followed by discussions of prematurity, complications of labor, and complications of pregnancy as nonspecific agents connected with later mental disorder or deficiency. The literature on descriptive associations between month of birth, birth order, maternal age and other descriptive characteristics are also reviewed. While the evidence relating a

number of infections is sufficient to justify preventive action, Dr. MacMahon makes it clear that many of the details are obscure and that evidence is lacking which would link number of agents which are otherwise known to be potentially harmful to the increased risk of mental abnormality. In particular, little is known about the increased risks associated with conditions which do not show manifestations of disorder in the perinatal period.

III. *George James, M.D.: The Epidemiology of Mental Disorder Associated with Damage to the Brain After Birth.*

Jaundice, anoxemia, ischemia, trauma, many poisons (including alcohol) and not a few of the medicinal drugs, and several infections, have been associated with temporary or permanent impairment of mental functioning as have a number of dietary and endocrine deficiencies, epileptic convulsions and cerebral arteriosclerosis. The epidemiological evidence for these causal links is reviewed and it is emphasized that very often the available evidence lacks refinements which would be desirable. Dr. James concludes that the greatest number of mental patients who suffer from organic brain damage were damaged from diseases which we still do not know how to prevent.

IV. *John Cumming, M.D.: The Family in Mental Disorder.*

This "incomplete essay" (so-called since it reviews only a portion of the very large number of studies which have tried to link the development of a mental disorder with a particular characteristic of the patient's family or family member) goes into less detail in criticizing the methodology of these investigations than in pointing out that the questions have often been too imprecisely stated to make research productive of answers. Dr. Cumming's discussion seeks to mark out a path through the present chaos in the field and to suggest ways of relating the studies to one another so that future investigations will be more productive.

V. *D. D. Reid, M.D.: Precipitating Proximal Factors in the Occurrence of Mental Disorders.*

This review concludes that the field lacks any sustained and sys-

tematic approach to the problem of precipitating factors. Dr. Reid believes that while the most valuable studies have been made of stress in wartime, events which occur in civilian life have not been absolved: they have only been insufficiently examined.

VI. *H. Warren Dunham, Ph.D.: Social Structures and Mental Disorders.*

The evidence which links an individual's position in the social structure in which he lives to the risk of manifesting mental disorders is examined; and a number of critical studies are woven into a reasoned discussion of both methodological and theoretical issues. From this evidence it is clear that the relationship between social class position, occupation, and a number of other similar factors, and the frequency of certain mental disorders (in one or another form of treatment) is very marked and well established. The causal meaning of these associations is still uncertain. The problems connected with exploiting the clues suggested by these associations, and the problems involved in closing the gaps in our knowledge about them, are amply classified and clarified, both by Dr. Dunham and by the group in the ensuing discussion.

VII. *H. B. M. Murphy, M.D.: Social Change and Mental Health.*

Since the Enlightenment it has been repeatedly claimed that rapid social change was productive of mental disorders. The evidence advanced in support of this thesis, is separated into two concepts: 1. Change as a specific factor in the production of certain cases of mental disorder. 2. Change that is disturbing to everyone but which produces a clinical form of the illness only in presently or potentially sick persons. This extensive review of the very large literature on migrating populations and populations undergoing social change now permits one to ask many different and more precise questions. Dr. Murphy concludes that non-Western peoples undergoing Westernization show an increase in identified psychopathology. However, whether this is due to an increase in prevalence or to improved facilities or other factors is not clear. The problems of investigating these questions are dealt with at some length.

VIII. *Alexander H. Leighton, M.D.: Cultures as Causative of Mental Disorders.*

Eleven different ways in which culture is thought to increase the frequency of particular mental disorders is examined and a review of the evidence for each type of linkage is examined separately. This classification is expounded together with examples of studies, no one definitive, which are directed at testing each theory. The fact that a global, cross-cultural classification of mental disorders does not exist is discussed as a gap in the technical resources for studying these issues.

PHYSICAL DAMAGE TO THE FETUS

BRIAN MACMAHON, M.D. AND JAMES M. SAWA, B.S.

INTRODUCTION

THE literature on prenatal influences in mental disease is voluminous, although perhaps less so than in some of the other areas of investigation discussed at this meeting. Some idea of its extent may be derived from the extensive reviews recently presented by Masland (145, 143). We do not propose, therefore, to be comprehensive in this discussion but have selected a number of areas in which there seems to be either the actuality, or the potential, of demonstration of significant prenatal or perinatal etiologic influences in mental disorders.

We have not interpreted any of the three major words in the assigned title of this article in any limiting sense. Thus "physical" is taken to include biochemical, biologic and any other possible mechanisms of action; "damage" includes all fetal effects that might conceivably be categorized as "mental"; and "fetus" is interpreted in such a way as not to exclude discussion of factors possibly exerting their effects during labor or in the general perinatal period.

Evidence relating mental disorder to factors operating during pregnancy or delivery will be considered at the following levels:

1. Direct evidence that fetuses known to have been exposed to specific agents have a greater frequency of mental disorders than those not exposed.
2. Evidence of unusually high mental disorder rates among special groups believed to have suffered high rates of exposure to deleterious prenatal or perinatal influences the exact nature of which is unknown.
3. Evidence of differences in mental disorder rates between subgroups of the population which may, or may not, be explicable in terms of differences in intra-uterine environmental experience.

This approach requires the discussion of a wide variety of mental abberations under the same heading. The alternative—the subdivision of the paper according to the major varieties of mental abnormality—was initially attempted but abandoned, since many of the studies to be described contain data pertinent to a variety of mental disorders. At the same time, every effort has been made not to confuse methodological evidence relevant to different forms of mental disorder. In particular, quite separate considerations will be taken of the following general categories of disorder:

1. The chronic brain syndromes, including anencephaly, hydrocephaly, microcephaly, mongolism, cerebral paralysis, etc.
2. Impairment of function as determined by intelligence tests not associated with a clinical neurological syndrome, referred to for the sake of brevity as mental retardation.
3. The functional mental disorders, including the psychoses, psychoneuroses, addictions and personality disorders.

Damage Due to Specific Agents

The evidence reviewed in this section is of importance not so much because of the numerical significance of the cases of mental disorder that can be ascribed to specific agents, but because of the demonstration that some success has been achieved in identifying such factors and the consequent implication that more remain to be identified.

SPIROCHAETA PALLIDA

Chronic Brain Syndromes. There is no evidence to link intrauterine syphilis infection with the congenital malformations or with the other common brain syndromes. However, congenital syphilis is associated clinically with its own characteristic brain syndromes. The belief that certain neurological signs seen in congenitally syphilitic children are the result of syphilitic infection depends on the similarity of certain of these signs to some of the neurological syndromes of acquired central nervous system syphilis (e.g., "juvenile tabes") or on the specific and characteristic nature of some of the signs (e.g., Argyll Robert-

son pupils). The frequency with which neurological syndromes are seen in prenatally infected children varies with such obvious factors as age of the patients at observation and age at which treatment is begun. Early studies report relatively high frequencies of neurological defects (e.g., 26 per cent of 202 congenital syphilitics (217) but Hallgren and Hollstrom (88) reported only 18 such cases among 219 congenitally syphilitic children of whom the majority received treatment prior to one year of age. When neurological signs are present the frequency of associated mental retardation is very high (e.g., 17 of Hallgren and Hollstrom's 18 cases).

Mental Retardation. The question of whether congenital syphilis is productive of mental retardation in the absence of neurological signs may be considered still open. The question has been attacked in the two classical epidemiologic ways—in case history studies of mentally defective children to determine the frequency of a syphilitic history, and in cohort studies of patients with congenital syphilis to determine the frequency of mental retardation.

From case history studies of mentally retarded children a range of frequency of congenital syphilis between 0.3 per cent (89) and 10 per cent (177) has been reported, with the majority of the values in the larger studies lying between 2 and 5 per cent (17, 124, 233, 50, 165, 175, 204, 135). The problem in the interpretation of these findings is, of course, the lack of suitable comparison groups, since, although the figures seem *a priori* to be higher than the frequencies of congenital syphilis to be expected in general populations of not mentally retarded children, congenitally syphilitic children carry many biologic and social disadvantages besides syphilis. For example, Benda (17) found 38 of the mothers of 76 retarded congenital syphilitic children to be themselves feeble-minded. Thus even where comparisons have been made with the frequency of congenital syphilis or of syphilitic pregnancy in the general population, one cannot be confident that the comparison adequately assesses the biologic effects of prenatal syphilis alone. Such

comparisons as have been made with general population data do not indicate particularly high frequencies of congenital syphilis among the mentally retarded (233, 50). Paddle (165) found a slightly higher frequency of congenital syphilis among mentally retarded children who exhibited epilepsy or physical defects than among uncomplicated cases.

In cohort studies, also, the question of finding a suitable comparison group is crucial and not yet solved. A number of early studies reported high rates of mental retardation among congenitally syphilitic children but did not report on comparison groups of any sort. Some of the types of comparison that have been made in later studies include:

1. Comparison with collateral estimates of the frequency of mental retardation in the general population. Hallgren and Hollstrom (88) in a followup study of 259 cases found a frequency of mental "deficiency" of 15.8 per cent compared to estimates of 1 to 2 per cent in the general population. Mental "subnormality" occurred in 36.7 per cent of the cases compared to population estimates of 7–9 per cent. However, for reasons given above, general population figures do not provide satisfactory comparisons.

2. Comparison according to type of treatment received (usually determined by date of treatment), with the belief that later treatments are generally more effective. Scheer and Stieler (201) and Lenstrup (126) report series in which there is little difference between treatment groups in the frequency of severe mental retardation, but in which the frequency of minor retardation is greater among those receiving the less effective treatment. These differences were not statistically significant. The only authors who have made allowance for differences between treatment groups in age at observation, Hallgren and Hollstrom (88), found in 219 cases no difference in the frequency of mental abnormality between five treatment groups ranging from mercury alone to penicillin plus other forms of treatment.

3. Comparison according to age at first treatment, early treatment being presumably more effective than late. Kundratitz (120) found 8 mentally subnormal among 60 children

treated in infancy compared to 26 mentally subnormal among 66 children treated after infancy. Kiss and Rajka (112) also found a substantial difference between cases treated under 2 years of age and over 2 years, but the number of cases is very small—11 and 34, respectively. Hallgren and Hollstrom (88) noted almost identical frequencies (19 per cent) of mental deficiency among 161 patients treated in the first year of life and 58 treated later.

The latter authors also compared the frequency of mental retardation according to whether or not the mother had received anti-syphilitic treatment during pregnancy. Paradoxically, the frequency of mental deficiency was almost twice as high (28 per cent of 46 cases) in those cases in which the mother had been treated during pregnancy as in those in which she had not (15 per cent of 138 cases). The authors dismiss this difference as being not statistically significant when separate examinations are made according to age at observation, but in the separate age-at-observation categories the difference remains and its lack of statistical significance is probably attributable to the small number of cases in these categories rather than to a reduction of the relative size of the difference. This finding offers a prime reminder of the fact that, in measuring postnatal effects in relation to prenatal influences, our measurement is one of prevalence and not incidence, and is consequently dependent not only on risk of occurrence of the unfavorable event but also on its duration. Thus, if maternal treatment increased the survival of defective children, it might be associated with an increase in prevalence of defective children measured postnatally even though the incidence of children *becoming* defective remained the same.

Even if a difference in mental status according to age at treatment had been demonstrated consistently (and it has not), one would still be faced with the problem of the self-selection of those presenting for early treatment. Hallgren and Hollstrom (88) found no difference between the mental conditions of mothers who received treatment during pregnancy and those who did not. Unfortunately they did not compare the mothers of children receiving treatment in the first year with those of children receiving later treatment in this respect.

4. Comparison according to the presence or absence of signs of congenital syphilis, the infection having presumably been more severe in children showing clinically recognizable signs. As already mentioned, the frequency of mental retardation in children showing neurological signs is very high. This was confirmed in a cohort study by Jenkins *et al.* (102). An interesting study of this type is the comparison by Hollgren and Hollstrom (88) of 328 patients with manifest congenital syphilis in a special home for syphilitic children with 172 patients admitted to the same institution in whom the diagnosis of congenital syphilis was in doubt. The authors state that the frequency of mental deficiency is higher in the first group than in the second. The exact meaning of some of the tables in this publication is obscure, but, so far as we can determine from the data presented, this statement is true only for patients under three years of age. The frequency of "mental subnormality" in patients over three years of age appears to be almost identical in the two groups.

5. Comparison with non-syphilitic siblings. This seems to be the most satisfactory comparison so far considered. Yet, presumably because of practical difficulties, it appears to have been used but once and then in a very small series. Jenkins *et al.* (102) found a lower average I.Q. among 24 cases of congenital syphilitic children than among their siblings, but the difference is not statistically significant.

In summary, we have been unable to find satisfactory evidence that prenatal syphilitic infection is causatively associated with mental retardation in the absence of the more severe neurological syndromes occasionally found in that disease. The virtual extinction of congenital syphilis in the major centers of medical research makes unlikely the provision of more convincing data in the future.

Functional Disorders. The problem of separating the effects of spirochaetal infection from the other concomitants of congenital syphilis is even more serious in interpreting the frequency of the behavior disorders and other functional conditions among such children than in studies of mental retardation.

The association between family disorganization and congenital syphilis has been dramatically shown by Jenkins and Crudim (103) who attribute the high frequency of behavioral disorders among syphilitic children to such concomitant disadvantages rather than to syphilis *per se*. The very high proportion of illegitimate children among such patients (118) is but one example of such a disadvantage.

Hallgren and Hollstrom found a higher frequency of behavior disorders among congenital syphilitic patients who had reached adolescence than among the general population (there is no evidence that similar scales of measurement have been applied) but no evidence of difference between syphilitic children of school age and the "average" school population. There was little difference at any age between their cases of definite and doubtful syphilis. If anything, the patients of adolescent age with questionable diagnoses had a slightly higher frequency of behavioral disorders than the cases with definite diagnoses.

Toxoplasma

Chronic Brain Syndromes. The first unequivocal case of human infection with toxoplasma was reported by Wolf *et al.* in 1939 (241), although in retrospect it was considered that four similar cases reported previously could probably be ascribed to this organism. All five cases were infants. Wolf *et al.* believed that the infection occurred *in utero* in view of the early age at onset in all cases (2 days to 7 weeks) and the advanced pathologic state of the central nervous system lesions found at autopsy. Vail (227) believed that, of the 12 cases of toxoplasmic chorioretinitis reported before 1943, 11 were congenital. This view has been upheld by later workers, and has been supported by (a) the observation that in cases of infantile and childhood toxoplasmosis, antibodies can almost invariably be found in maternal blood (198, 136), and (b) the frequent occurrence of malformations such as microcephaly and microphthalmus that indicate infection quite early in pregnancy, and even the occasional prenatal diagnosis of a lesion (hydro-

cephalus) subsequently diagnosed as due to toxoplasma (242). At least one case of isolation of toxoplasma from an abortus has been described (79).

Like most, if not all, of the specific agents known to produce fetal damage, toxoplasma is associated with a characteristic brain syndrome. The characteristic features of congenital toxoplasmosis are chorioretinitis and cerebral calcification. Hydrocephaly, microcephaly, microphthalmus, convulsions, mental deficiency and a variety of serious neurological disorders may be present but are not characteristic. The combination of chorioretinitis and cerebral calcification is associated with toxoplasmic infection in a very high proportion of cases (perhaps in 90 per cent (199)), but children exhibiting one of these signs alone or in combination with the one of the other signs indicated above rarely have positive serological tests (198, 136, 199). It is not likely, therefore, that toxoplasma infection is associated with such brain syndromes as hydrocephaly and microcephaly except when these occur with the more characteristic features of the syndrome.

The proportion of symptomatic human toxoplasmosis that is due to prenatal infection is not known. Most cases in infants and young children are so ascribed on the basis of the extensive damage found (and implied long duration of infection). There is an increasing tendency to ascribe cases in older children to prenatal infection with early quiescence and subsequent recrudescence due perhaps to rupture of a pseudo-cyst (166). This possibility is suggested by the observation that chorioretinitis occurs routinely in childhood toxoplasmosis but is rare in the acquired disease of adults, and the fact that a certain number of congenital cases are undoubtedly quiescent for some time. In adults, for example in the mothers of affected children, toxoplasmic infection appears to be usually symptomless although a few cases with symptoms have been described.

As an asymptomatic infection in adults toxoplasmosis is fairly widespread; for example 5 per cent of a group of adults in North West England showed serum antibodies (136). These cases

must be considered acquired since antibodies are rarely found in normal children (136, 199). The question might therefore be raised as to why prenatal infection is such a comparatively rare occurrence. Sabin and Feldman (199) noted that subsequent children born after a child with toxoplasmosis are normal even though the mothers maintain high titers of antibody. These observations have been explained by MacDonald (136) in terms of trans-placental transmission of maternal antibodies without simultaneous transfer of infection, a phenomenon noted also by others (79, 199). MacDonald suggested that the protective effect of antiserum is extended to the fetus and that the fetus is infected only if the mother is infected during pregnancy or so recently that her antibodies have not yet developed.

Much remains to be clarified regarding the mechanism of toxoplasma infection, the frequency of the asymptomatic congenital disease, and the probability of eventual symptoms among asymptomatic prenatally infected children.

Mental Retardation. As noted, the toxoplasma syndrome is characteristic and it does not seem likely that toxoplasmosis is causally related to undifferentiated mental retardation. Burkinshaw *et al.* (34) performed toxoplasmin tests on 698 mental defectives. The per cent positive increased regularly with age, from zero at ages 0–4 (65 cases) to 58 at ages 50–60 (12 cases). No particular clinical pattern was noted among the 55 positive cases. It was concluded that these were all acquired infections and that such infection was no more common among mental defectives than among the general population.

Rubella

Chronic Brain Syndromes. Maternal infection with rubella during the first trimester is also associated with its own characteristic fetal syndrome, comprising congenital cataract, deafness, and, less characteristically, congenital heart disease and microphthalmus. The most critical examination of this association is the summary by Hill *et al.* (93) of their own study and three similar cohort studies (32, 31, 184), which suggest

that the frequency of major fetal defects may be in the order of 50 per cent, 25 per cent, 17 per cent and 0 per cent for infections occurring during the first, second, third, and fourth or later intra-uterine months, respectively.

The brain syndrome established as a likely (though inconstant) part of the rubella syndrome is microcephaly. In reviewing the literature prior to 1949, Swan (219) found 128 cases of microcephaly associated with maternal rubella. Among 9 malformed children with a history of maternal rubella Albaugh (4) found 5 definitely microcephalic. The attribution of the microcephaly to maternal rubella in these cases is lent credence by the fact that 8 of the 9 cases also had the characteristic bilateral cataracts. One case of microcephaly associated with cataract (184) was reported in one of the four cohort studies reviewed by Hill *et al.*, among 50 infants in which rubella occurred in the first trimester.

Other brain syndromes have been reported much less frequently than microcephaly, in spite of the fact that most of them are much more common than microcephaly in general experience. Swan (219) noted in the literature 8 cases of mongolism associated with rubella. In the four cohort studies (104 patients infected at all stages of pregnancy) mongolism and anencephaly occurred once each, although, since the months of pregnancy at which the infection occurred were the fourth and fifth respectively, it seems likely that the association with rubella was fortuitous. Interestingly, these same malformations occurred once each in the 90 controls of a recent study of Siegel and Greenberg (207), but not in the children of 80 women with viral infection during pregnancy. Case history enquiries in two large series of cases of anencephaly did not reveal any case of maternal rubella during pregnancy (189, 44).

Mental Retardation. Mental retardation has been frequently mentioned either as a concomitant of other components of the rubella syndrome or as an isolated result of maternal rubella.

Kirman (111) reported a definite history of maternal rubella in 7 of 791 cases of mental deficiency. In 5 of these the child

also showed cataract, deafness or both. In these five cases the infections occurred in the first trimester of pregnancy. In the other two cases the rubella occurred during the fifth and second month of pregnancy, respectively. No comparison group was used. Of course the characteristic lesions of fetal rubella (blindness and deafness) are such as are likely to be accompanied by apparent mental incapacity, although whether physical brain damage occurs independently of the other lesion is not certain. Mental defect was not a feature noted in the patients in the cohort studies reviewed by Hill *et al.*, but no special effort was made to ascertain this defect. Later studies are planned by at least one of the groups (32). It must be concluded that, at the present time, there is no evidence that prenatal rubella infection predisposes to mental retardation in the absence of the other characteristic features of the syndrome.

OTHER INFECTIONS

Earlier suggestions, based on isolated case reports, that a variety of other infections, including mumps, infective hepatitis, measles and chicken pox, might be associated with fetal defect have not been substantiated by later cohort studies (93, 207). Larger studies are in progress (207).

IONISING RADIATION

Chronic Brain Syndromes. A microcephalic child following deep X-ray therapy of maternal myomata during the first four months of pregnancy was reported by Aschenheim in 1921 (8). In 1929 Murphy (157) assembled reports of 106 cases of maternal pelvic radiation during pregnancy and of 519 women who became pregnant subsequent to irradiation by a review of the literature (155) and by sending a questionnaire to 1,700 gynecologists and radiologists (156). The striking feature of the data is not the high frequency of malformations among the children irradiated *in utero,* since in view of the method of collection of the data it would not have been too surprising if all had been affected, but the predominance among the affected of

one syndrome—among 74 liveborn children irradiated during pregnancy, there were 25 with major malformations of which 17 had microcephaly.

Additional data have been obtained from women who were pregnant at the time of the bombing of Hiroshima and Nagasaki. In Hiroshima 7 infants with microcephaly were born to 11 women exposed within 1,200 meters of the hypocenter but no such cases were seen among 194 women exposed at distances greater than 1,200 meters (186). In Nagasaki one case of definite microcephaly was found among the children of 16 mothers who experienced signs of major radiation injury (245). The difference in rate for the two cities is in part due to the fact that in the Hiroshima study only pregnancies in the first trimester were considered; only 7 of the 16 Nagasaki mothers were in the first trimester. In addition, in Nagasaki, the mean head circumference of the 16 children was significantly smaller than that of the children of mothers who were also within 2,000 meters of the hypocenter but did not have signs of major radiation injury (57 children) and also of that of the children of mothers exposed outside of 2,000 meters (96 children).

It cannot be doubted that large doses of ionising radiation during pregnancy are associated with high risk of microcephaly in the child. However, the rarity of deliberate radiation early in pregnancy makes this an extremely rare cause of congenital malformation at the present time. No brain syndrome other than microcephaly can be convincingly related to *in utero* irradiation, although among the 11 Hiroshima children exposed within 1,200 meters there were two cases of mongolism. This malformation does not feature in the isolated reports of defects following medical radiation, being noted only once by Murphy (157).

Mental Retardation. In addition to the child with microcephaly there were 3 other mentally retarded among the 16 heavily exposed Nagasaki children, but none among the 153 lightly exposed. Otherwise there is no evidence relating ionising radiation to undifferentiated mental retardation in man. In

rats, Furchtgott *et al.* (78) and others (133) have shown that learning ability is seriously affected by both prenatal and neonatal irradiation, and that the severity of the defect is related both to time of intra-uterine exposure and dose of irradiation.

While deliberate radiation during the early months of pregnancy is very rare, all pregnant women experience the normal levels of radioactivity from natural sources. Consequently, evidence of fetal effects associated with exposures to radiation at the levels with which background radiation varies from place to place would be of considerable significance. The recent study of Gentry *et al.* (80) deserves comment therefore, since, while not directly pertinent to mental disorders, if the observations relating to major congenital malformations were confirmed, the next logical step would be similar investigations of less obvious defects, including undifferentiated mental retardation.

Gentry *et al.* noted that, grouping areas of Upstate New York according to the probability of high natural occurrence of radioactive elements in the underlying geologic formations, rates of congenital malformation (as determined from certificates of birth and death) were higher in those areas in which high levels of radioactivity were probable (15.1 malformed infants per 1,000 livebirths) compared with areas in which extensive deposits of radioactive elements were unlikely (12.8 per 1,000). In favor of the hypothesis of direct relationship between background radioactivity and malformation rates are the following: (1) the remarkable consistency of the difference, it being noted for both urban and rural areas, within each of the six standard geographical regions of the State (at least for the rural areas of these regions), and for each of five paternal occupational groups; (2) the relationship is more evident in groups who would be expected to experience heaviest exposure, being more striking in rural than in urban areas and in rural areas in which the water supply is from wells and springs than in rural areas with surface supplies (in fact, rural areas with surface supplies even when located within areas of probable extensive radioactive deposits have rates similar to areas of unlikely deposit);

and (3) examinations of a large number of variables including consanguinity, ethnic background, family reproductive history, etc., are said not to have revealed any alternative explanation of the differences noted, although the nature of these examinations is not detailed. In cautionary vein it should be noted that: (1) the total prevalence rates derived suggest that the sources of data used are identifying only perhaps 50 per cent of the major malformations occurring (depending on one's definition of a major malformation); (2) data on stillbirths are not included, much less those on early fetal deaths, and possible differences in selective loss of deformed infants are therefore not revealed; (3) the correlation between maps of malformation rates and geological formations which seems so obvious to the authors is not at all clear, at least to us; (4) the observations depend essentially on a high malformation rate noted among 15,307 livebirths (259 malformed) in 255 rural communities obtaining water from wells and springs; such communities must be typical in many respects and one cannot feel completely satisfied with general statements about examination for the effects of other variables, particularly when marked differences between the "probable" and "unlikely" areas are evident in certain of the tabulations (for example, of paternal occupation); and (5) it is strange that the relationship should hold for all of nine diagnostic categories of malformation with the exception of mongolism; past studies have pointed more and more to the specificity of action of teratogenic agents in the laboratory animal (237) and to major difference in the epidemiologic characteristics of different malformations in man.

It is clear that this intriguing observation is in urgent need of further investigation, preferably in other geographic areas.

JAUNDICE

Chronic Brain Syndromes. Jaundice of the nuclear centers of the brain associated with neurological symptoms was described in 1875 (163). Cases appeared in the English literature

in 1913 (87) and 1915 (215) but the syndrome was not widely recognized until comparatively recent times; by 1940 only 15 cases had been reported (214). In 1937 Klingman and Carlson, noting 45 instances of severe neonatal jaundice in the histories of 675 children with severe neuromuscular dysfunction, suggested that the syndrome may be more frequent than was generally thought (113). By the end of the next decade individual series of 26 to 37 cases were being reported (228, 41), mostly in association with erythroblastosis fetalis. A very high proportion (about 70 per cent) of obviously affected infants die in the first few days of life (228, 41, 94). The syndrome in surviving infants includes a variety of neurological lesions and mental retardation. Experimental evidence that in rats bilirubin is both the toxic and the staining agent has been provided by Johnson *et al.* (104).

The effect is not strictly a fetal one, since the damage usually occurs in the first day or two of life. This is suggested by the fact that neurological symptoms are not present at birth but develop most commonly on the second day of life (94), kernicterus is not seen in jaundiced infants who die within a few hours of birth (41, 42), and the frequency of kernicterus is apparently greatly reduced by exchange tranfusion (109, 236, 6).

The frequency of this complication of jaundice varies with the type and severity of jaundice reported and the efficacy of the treatment. In erythroblastosis, frequencies of 55 per cent (56), 34 per cent (41), and 12 per cent (228) have been reported. Relating the frequency of kernicterus to the level of the infant's serum bilirubin, Hsia *et al.* (94) report frequencies between zero in the range of serum bilirubin 0–5 mgm per cent to 50 per cent in children with serum bilirubins above 30 mgms per cent. Kelsall and Vos state that in their experience kernicterus has become so rare in incompatible pregnancies treated by induction and exchange transfusion as to be "practically never seen" (109, 110). Armitage and Mollison report frequencies of 41 per cent in 54 infants receiving simple trans-

fusion and 20 per cent in 60 infants receiving exchange transfusion (6). Kernicterus in infants jaundiced for reasons other than erythroblastosis has been reported by Docter (56) and Govan and Scott (86).

Mental Retardation. The fact that the signs of kernicterus vary from mild motor incoordination with normal intellectual function to severe motor disorders with idiocy suggests that less obvious defects, including undifferentiated mental retardation, might follow less serious or more localized damage. Authors with considerable clinical experience have stated that the signs of kernicterus are so characteristic that the diagnosis can be made or excluded during the first week of life (228). However, in a followup study Jones *et al.* (106) found 3 children with definite and 2 with equivocal neurological abnormality among 76 erythroblastotic children considered normal in the neonatal period. Armitage and Mollison also report 4 cases who appeared normal at one month of age and who either died of kernicterus (one case) or were retarded at the time of followup (6). Gesell tests were included in the evaluations in the study of Jones *et al.* but results are not given in the article.

Yannet and Lieberman (247, 248, 249) obtained blood samples of the mothers of 277 children with I. Q.'s less than 30 and of the children when the mothers were Rh negative. One hundred fifty-eight of these children fell into recognized diagnostic sydromes and 119 were undifferentiated. There were 14 per cent Rh negative mothers in the recognized syndrome group, which agrees with expectation. This frequency of maternal Rh negativity should produce an expected maternal-fetal incompatibility rate of 8.2 per cent, which is close to the 7.6 per cent found. In the undifferentiated group, 22 per cent of the mothers were Rh negative and 16 per cent of the mother-child relationships were incompatible. Nineteen cases of mother-child incompatibility were found, compared to 9 expected. In 6 of these 19 cases, evidence of maternal Rh isoimmunisation was found; all these infants were jaundiced in the

neonatal period. No such evidence was found in the other 13 cases, although the histories were not all adequate to rule out the possibility. It is of interest that all 6 infants with erythroblastosis had significant neurological signs. Histories of the other 13 cases are not given in detail, but it is stated that the physical findings were characterized by absence of signs of central nervous system involvement except for the mental defect. Without the 6 cases of neurological defect the excess of incompatible pregnancies is not statistically significant.

Gerver and Day (81) compared 68 children who had erythroblastosis, with their elder first-born siblings. The 68 patients, did not include any with "obvious motor nerve damage." The 68 patients, at an average age of 4.5 years, had an average I.Q. of 102.7. Their first-born siblings, at an average age of 9.8 years, had an average I.Q. of 114.5, significantly higher than the patients. The authors found no difference between older and younger in 28 pairs of normal siblings who were said to have a similar age difference to that between the patients and their comparison siblings. However, the possibility that a difference between birth orders might contribute to the observed difference between siblings has not been completely ruled out. The relationship between I.Q. and order of birth is complex and, since the two groups were drawn from different sources, the absence of a relationship in one situation does not rule out its existence in the other.

In summary, the evidence to date indicates that if neonatal jaundice is productive of mental defect without neurological signs such cases are probably rare.

ASPHYXIA

In a later section evidence will be presented that a variety of difficulties in labor are likely to be followed by an increased frequency of mental and neurological disorder. This and the subsequent section deal with two specific mechanisms, anoxia and trauma, whereby difficulties of labor might produce their effects. It is, of course, extremely difficult to separate the in-

dependent effects of anoxia and trauma, since infants with one frequently also have the other. For this reason it seemed desirable to consider birth difficulties as a non-specific experience without prejudice as to their mechanism of action. Only studies dealing specifically with anoxia or trauma are discussed in this section.

The problem of the differentiation of anoxic and traumatic effects also arises in pathologic discussion of the problem of birth injury. Thus, although it is generally agreed by pathologists that multiple minor cerebral hemorrhages are associated with cerebral damage following birth injury, Schwartz (205) and other early reporters of these lesions (197) attributed them to mechanical causes. Later pathologists attribute the same lesions to anoxia (188). It seems likely that both mechanisms are involved (48).

Trauma and mechanical asphyxiation are probably the most frequent causes of fetal anoxia. Maternal sedation and anesthesia must also be considered as important causes of fetal anoxia (43, 224, 243), although we have not encountered any studies of the relationship of mental defect to this cause of anoxia specifically.

Chronic Brain Syndromes. Case history studies of series of children with cerebral palsy and epilepsy have indicated high frequencies of neonatal asphyxia. Schreiber reports neonatal asphyxia in 70 per cent of 900 children with neurologic signs (excluding those in whom "inherited defect, postnatal trauma or infection" were suspected) (203). Skatvedt, among 355 patients with cerebral palsy, found 26 per cent with "protracted" initial apnea and a further 18 per cent with asphyxial attacks occurring after initial respiration (200, 208, 209). On the other hand, figures as low as 15 per cent have been suggested as estimates of the proportion of cerebral palsy cases attributable to asphyxia (53). Eastman and DeLeon, in one of the few controlled studies (62), compared 96 children with cerebral palsy with 11,195 surviving normal children. Seventeen per cent of the palsied children did not breathe until

four or more minutes after birth, compared to 0.7 per cent of the normal children. Thirteen per cent of the palsied children did not breathe for six minutes or more, compared to 0.3 per cent of the normal children. These data would suggest an incidence of cerebral palsy forty times higher in those who did not breathe for six minutes or more than in those who breathed within six minutes. Complications of anaesthesia were noted in 4.2 per cent of the cases and 1.0 per cent of the normal births.

It has also been suggested that asphyxia is found frequently in the histories of children with epilepsy (160) and "chronic degenerative disease of the brain" (240), although no control groups were incorporated in these studies, and the evidence is not so striking as in cerebral palsy.

Windle has produced neurological damage in guinea pigs by constriction of the maternal uterine vessels near term. The more prolonged the asphyxiation the more marked and more persistent were the signs of brain damage. At autopsy capillary hemorrhages were seen, but neuronal damage was encountered even when no capillary extravasations had occurred (238, 239).

It must be accepted that fetal anoxia in the perinatal period is associated with increased risk of neurological damage. However, further quantitation of the relationship and elucidation of the effects of anoxia in the production of minor neurological damage would seem to depend on more detailed cohort studies such as the Cerebral Palsy Collaborative Study of the National Institute of Neurological Diseases and Blindness (144). Particular attention might well be focused on infants who experience anoxia but in whom the probability of physical trauma is not higher than normal.

Fetal defects, mostly skeletal in nature but including anencephaly, have been produced in mice by severe maternal anoxia during pregnancy (98, 97). There is no evidence that such a mechanism operates in man to produce those brain syndromes that are determined early in pregnancy.

Mental Retardation. It has been shown by Windle (238, 239) and Becker (15) that guinea pigs asphyxiated at birth are inferior in maze learning and retention to control litter mates. Two small followup studies in man (of 19 (49) and 61 (35) cases, respectively) have also indicated evidence of poorer intellectual function among asphyxiated infants than among comparison groups. In the latter study the difference was not statistically significant; descriptive groupings were used in place of I.Q. Courville and Marsh state that mental deficiency alone or in combination with neurologic defects is the most common result of clinical neonatal asphyxia (47). They state that most surviving infants show some mental deficit, but the data forming the basis of this experience are not given.

Clearly, here is another area requiring additional data from carefully designed cohort studies.

TRAUMA

While asphyxia may arise from conditions, such as constriction of the cord, that are not associated with trauma, the reverse situation is rare. Consequently it is very difficult to assemble evidence that trauma in itself is productive of neurologic abnormality. Most studies have dealt with methods of delivery in which trauma is probable; these are discussed in a later section. There is remarkably little evidence to indicate the amount of neurological damage following difficult delivery that is directly attributable to the trauma and not to the accompanying asphyxia, or to indicate the possible effects of minor traumatic experiences not associated with gross cerebral hemorrhage.

Nevertheless, physical trauma is *a priori* the most obvious form of fetal damage and its effects can hardly be doubted. Major cerebral hemorrhage associated with tentorial tears and ruptures of the cerebral venous system that can only have been traumatic in origin have been described by many pathologists (197, 37, 68). Such clearly traumatic injuries are associated

particularly with high forceps delivery. Bundesen *et al.* in a large series of autopsies found traumatic cerebral hemorrhages in 55 per cent of cases delivered by mid or high forceps, in 22 per cent of those delivered in low forceps and in 14 per cent of those delivered spontaneously (33). Among 55 cases of subdural hematoma reported by Elvidge and Jackson (68) there were 9 definitely attributable to trauma (as revealed by skull fracture in 6 and tentorial tear in 3) and a further 27 in which the delivery history made the diagnosis of trauma likely.

Cases associated with obvious trauma are, of course, the extreme ones. It is most likely that minor forms of injury also lead to damage. Such, for example, are the clinically well-recognized peripheral nerve palsies associated with specific methods of delivery. In the controlled cerebral palsy study noted above, Eastman and DeLeon (62) noted 26 per cent of the cases exposed to conditions conducive to mechanical trauma as opposed to 8 per cent of the controls.

SPECIFIC NUTRITIONAL DEFICIENCIES

Iodine Deficiency and Thyroid Disorders. The investigation of the relationship between goiter and iodine deficiency is pertinent here insofar as it relates to the etiology of congenital cretinism, a hormonal deficiency associated with severe mental retardation. Mental development is always subnormal in congenital cretinism. The fact that cretins receiving thyroid therapy prior to the age of six months attain somewhat higher intellectual development than those in whom therapy is delayed (213) suggests that some postnatal influence by replacement therapy is possible, but however early such therapy is undertaken a high frequency of mental subnormality still results (213, 85, 232).

It is established that simple goiter, whether congenital or acquired, is associated with dietary iodine deficiency. Other theories explaining the areas of high goiter endemicity, including linking the disease to high background radioactivity in

endemic areas (178, 123), have been discounted in the light of extensive experimental work (72, 141) and human mass therapeutic trials (142, 185, 65), although recent interest in congenital malformations and background radioactivity will, no doubt, renew the attention given this theory.

The fact that congenital cretinism of the endemic form is closely associated geographically with goiter suggests a similar causal mechanism. In Switzerland, Eugster (71, 70) states that his group has never found a case of cretinism in an area free of goiter, whereas in places with a goiter prevalence of over 50 per cent, prevalences of cretinism of 0.6 to 1.0 per cent have been noted. However, it is not clear whether fetal cretinism is directly associated with iodine deficiency (the goiters definitely attributable to iodine deficiency are hyperplastic) or whether the association is operative via maternal physiologic effects produced by the mother's own goiter. The fact that the mothers of cretins, at least in endemic areas (71), are themselves nearly always goiterous suggests that latter possibility. The Swiss experience notwithstanding, congenital cretinism, in both familial and non-familial forms, does occur in areas where iodine intake is adequate (244). However, so far as is known, maternal hyperthyroidism as it occurs in non-goitrous areas is not associated with fetal cretinism or other thyroid abnormalities.

Since the introduction of thiouracil in the treatment of hyperthyroidism, concern has been felt regarding its possible effects on the fetal thyroid. Experimental work suggests reasonable grounds for the concern. Thiouracil given to pregnant rats results in thyroid hyperplasia in the offspring (82). This hyperplasia is prevented if thyroid hormone is administered at the same time (77a), suggesting that maternal thyroid deprivation and not a toxic effect of the drug is responsible. If thiouracil administration is continued (e.g., via the mother's milk) the hyperplasia increases and cretinism eventually results (96, 77b). In man, several cases of congenital goiter following thiouracil treatment during pregnancy have been reported

(1, 29). Only two cases of hyperthyroidism in similar circumstances have been found (154, 67). In both cases the hyperthyroidism was transient; however, in both cases the child was mentally retarded at followup; in one, the child had hydrocephaly thought to be coincidental to the thyroid condition but not the cause of the retardation (154).

At this point, perhaps, mention should be made of the hypothesis linking maternal thyroid disease to fetal mongolism. This hypothesis has appeared in a variety of guises (158, 18), and has been most recently resurrected by Ek (66) who found higher blood protein iodine values among the mothers of a group of mongols than among a haphazardly selected "control" group. The evidence does not seem sufficiently convincing for detailed review, although it cannot be said that the possibility of maternal hormonal imbalance of some type being associated with fetal mongolism has been convincingly eliminated.

Copper. Swayback, a demyelinating disease of lambs, resembling in its pathologic picture Schilder's encephalitis, has been convincingly shown to be the result of maternal copper deficiency during pregnancy (100). It is prevented by the administration of copper to pregnant ewes.

Vitamins. Following the work of Warkany and Nelson on the production of congenital malformation in the rat by maternal Vitamin A deficiency (229, 230, 231), hydrocephaly and other cerebral malformations have been induced by a number of vitamin deficiencies, including riboflavin, folic acid, pantothenic acid, and Vitamin E (159). Hydrocephalus has also been produced in rabbits by maternal Vitamin A deficiency (149). Minor deficits as revealed by maze learning tests, have been noted in the offspring of rats fed on folic acid deficient diets (234).

Although there have been a number of controlled experiments on the results of vitamin supplements in pregnant women (63, 222, 21, 235), some with significant results so far as immediate outcome of pregnancy is concerned (221, 220), the

mental status of the offspring appears to have been considered only once (91). Harrell *et al.* conducted a controlled trial in two populations, one predominantly Negro, the other predominantly white. The treatment groups received: (a) ascorbic acid, (b) ascorbic acid, thiamine, riboflavin, and niacinamide, (c) thiamine and (d) placebo. The results of I.Q. determinations at age 3 years and age 4 years are suggestive but equivocal. In the Negro group (approximately 120 children in each treatment group) the offspring of the supplemented women had significantly higher I.Q's than those of the women receiving the placebo. There were no marked or significant differences between the various supplement groups. In the predominantly white group, which was somewhat larger (approximately 200 children in each treatment group), the placebo group actually had a slightly higher mean I.Q. than any of the treatment groups, but the differences were not significant. Possible reasons for the difference between the results in the two groups include the lower dietary baseline from which supplementation was begun in the Negro group, the slightly longer duration of supplementation in the Negro group (134 days compared to 114 days), and the rural nature of the white population that raised considerable difficulties in ensuring adequacy of administration of the supplements.

Significant increase in I.Q. associated with improvement in general nutrition occurring early in postnatal life has been claimed by Kugelmass *et al.* (119) on the basis of observational studies. Harrell, in a controlled trial, observed improvement in ability in a number of intellectual tasks following thiamine supplementation of the diet (90). These observations are indirectly relevant to consideration of the influence of the prenatal "diet."

Protein. There has been interest in the relationship of maternal dietary protein to immediate outcome of pregnancy (235, 211, 55); once again, none of these studies has been concerned with mental condition of the offspring.

Non-Specific Traumatic Experiences

PREMATURITY

Chronic Brain Syndromes. No note will be taken here of the frequent reports of association between prematurity and those chronic brain syndromes that originate in early pregnancy. When such associations exist, as they undoubtedly do, for example in the case of anencephaly and its concomitant hydramnios, it must be considered that the malformation is etiologically related to the prematurity, rather than vice versa.

The high frequency of cerebral palsy and its related disorders among prematurely born infants is well substantiated. It was noted by Little in 1862 (132). The literature has been extensively reviewed by Alm (5) in 1953 and by Polani (187) in 1958. Strong associations have been noted both in case history studies of spastic children (209, 62, 11, 40, 129, 131) and in cohort studies of prematurely born children and various comparison groups (5, 117, 153). The probability of neurological damage increases with the degree of prematurity as measured by birth weight. In a cohort study, Knobloch *et al.* (116) have shown a close association between physical and neurologic defects in premature infants and have suggested that the factors responsible for the increased frequency of cerebral damage in premature infants also have generalized deleterious effects.

In addition to noting a high frequency of children of low birth weight among a series of cases of cerebral palsy, Skatvedt also noted a percentage of children with very high birth weights (over 4,000 gms.) significantly larger than in a group of average hospital births (21.5 per cent compared to 15.5 per cent) (209).

Association of prematurity with convulsive disorders has received less attention. However, the frequency of epilepsy among premature infants does appear to be higher than among children of normal birth weight (5, 22, 58). The most convincing demonstration of this is in the study of Lilienfeld and Pasamanick (129, 171, 128), in which, in both white and

Negro patients, the percentage of children of premature birth was significantly higher among epileptic patients than among a comparison group selected from birth certificates.

Various mechanisms have been postulated to explain the striking association between prematurity and neurological damage. These include physical trauma associated with precipitate delivery, immaturity of the fetal anatomical structures, and higher frequency of abnormal presentations, anoxia initiated by immaturity either of the respiratory musculative (28) or of the respiratory enzyme mechanism (20), and kernicterus associated with greater frequency and severity of erythroblastosis (3) or with physiologic jaundice (2). A developmental mechanism (of unspecified nature) responsible for both neurologic damage and prematurity has been postulated (187), but in view of the many more obvious mechanisms this postulate hardly seems necessary.

Mental Retardation. A number of early studies which, because of either the high proportion of cases for which data are not available (202, 195), or because of the absence of adequate comparison groups (22, 61, 30, 9) did not give convincing results, will not be described although an overall impression of high rates of mental retardation among premature infants is gained from them. Pasamanick and Lilienfeld found a significantly higher proportion of prematurely born infants, both with and without maternal complications, among mentally deficient children than among a comparison group selected from birth registers (172).

Roberts and Asher (192, 10) compared the birth weights of children attending a normal school in a London borough with those of children attending special schools for the retarded and with those of a group of certified mental defectives. Over a wide range of birth weights (about 6 to 10 pounds) there was little variation in the birth weights of the three groups. Below 6 lbs. the retarded groups showed an excess compared to the normal group, which excess increased as the birth weight fell. At the lowest birth weights there were relatively

four times as many cases in the retarded groups as in the normal group. Interestingly, in the light of the observation of Skatvedt on cerebral palsy (209), there was also a significant excess of retarded children in the birth weight groups over 10.5 pounds.

In a small cohort study in Sweden, Blix and Holmdahl (25) compared 74 premature children with their siblings. The children born prematurely required special classes for mental retardation significantly more frequently than did their siblings. More substantial, and generally more adequately controlled, cohort studies have been reported in the last three years by Knobloch *et al.* (117), Douglas (57) and Drillien (59, 60). In these studies the prematurely born children showed a striking excess of mental retardation as measured by the number of grossly defective on Gesell development tests, or reading, vocabulary, and other mental ability tests. The probability of defect increases with the degree of prematurity (117, 60). The frequency of mental defect is increased in the prematures even in the absence of overt neurological damage, and vice versa (117). In one study, prematures from uncomplicated pregnancies (absence of toxemia, threatened abortion or induction of labor) showed lesser handicap than those from complicated pregnancies (57). On the other hand, Drillien found no definite indication of difference in ability at age two between prematures who had and had not abnormal neonatal signs such as cyanosis or apnea. The fact that, for a given degree of prematurity, first born were less retarded than later born (60) and children of small mothers were less retarded than those of large mothers (57), suggests that the defect is greater among genuinely "immature" deliveries than among infants with physiologically low birth weights.

Functional Disorders. Knobloch and Pasamanick (114) have reported a relationship between birth weight and adaptive behavior in a small group of Negro infants, children with higher birth weights being more advanced than those below median weight. In one of the few studies of prematures fol-

lowed into adult life, Alm (5) found a great many physical and social differences between the prematures and his comparison group but no appreciable differences with respect to frequency of criminality or alcoholism. No undue frequency of prematurity has been found among infants with stuttering (27) or speech disorders (168), or among children with tics (169). On the other hand, it has been suggested that premature infants experience a greater than average frequency of reading (107) and behavior (193, 173) disorders.

Reminiscent of the finding of Roberts and Asher on mental retardation and Skatvedt on cerebral palsy, is the report by Barry (12) of an unusually high proportion of birth weights over 9 lbs. among young adult patients admitted to hospital with psychosis and psychoneurosis. Although the data in this particular study are not convincing, being based on the memories of relatives and not being available for a high proportion of cases, the finding is an interesting one, seeming as it does to associate adult psychiatric illness with a characteristic evident at birth. The observation deserves further investigation.

COMPLICATIONS OF LABOR

Chronic Brain Syndromes. Difficulties of labor associated specifically with fetal anoxia or physical trauma have already been discussed. A great many workers have described the association of mental defect with difficult delivery without consideration of the mechanism whereby the defect is produced.

The clinical syndrome of neurological defect and difficult delivery is so well recognized that the association of the two in any one child is likely to be considered causative, particularly if the symptoms of neurological defect can be traced to the neonatal period. Among 370 cases of cerebral palsy, Skatvedt (200) found 19.3 per cent of breech presentations, 13.5 per cent of forceps deliveries, and 13.5 per cent precipitate deliveries. The percentage of breech deliveries seems very high, but no comparison group is available to evaluate the noted frequencies of forceps and precipitate deliveries. This author

also notes a high frequency of prolonged labor as reported by the mothers (37 per cent) but other controlled studies have not produced evidence of association of neurological damage with prolonged labor *per se* (62, 108). Ford (75) reports 15 per cent of cases of abnormal labor among 235 children with spastic paralysis, but once again no comparison group is examined. Asher and Schonell, among 221 term deliveries of children with cerebral palsy, found 39 per cent with abnormal deliveries. Twenty-four per cent were forceps deliveries and 15 per cent showed other abnormalities, whereas "normal" rates for these complications were supposed to be about 5 per cent for forceps delivery and 5 per cent for other abnormalities (11).

Dealing specifically with breech presentation, Churchill (39) reports frequencies of 30 per cent idiopathic epilepsy, 8 per cent in cerebral palsy, 5 per cent in mental deficiency and 3 per cent in the general population. From these series, cases "obviously" not originating in the paranatal period were excluded. Znamenacek *et al.* report four times as many cases of birth trauma among breech as among vertex deliveries (251). In the studies of epilepsy (128) and cerebral palsy (127) by Lilienfeld, Parkhurst and Pasamanick that are discussed below, the frequency of breech presentation was no greater in the epileptic children than in the comparison group drawn from birth certificates; nor do the data indicate any greater frequency in the epileptic group of other abnormal presentations or of "dystocia" due to other causes. However, among the children with cerebral palsy, an excess of breech presentations, other malpresentations and a variety of causes of dystocia is evident.

Mental Retardation. Analyzing data on retarded children in Massachusetts public schools, Dayton suggested that abnormal labor was found more frequently in "retarded" than in "defective" children (52). However, the differences noted were very small and the comparison data unsatisfactory. Benaron *et al.* (16) in rather small series (approximately 50

cases in each group) found no statistically significant differences in mental development between groups of children delivered by forceps and those from spontaneous normal deliveries and precipitate labors. A higher frequency of mental retardation was found in the group of precipitate deliveries, but this group is, of course, atypical with respect to birth order, family size and a number of other variables besides rapidity of delivery. In the data of Pasamanick and Lilienfeld (172) (*see* below) the children with undifferentiated mental retardation showed no greater frequency than the comparison group of breech delivery, dystocia due to abnormal pelvis or of other causes of dystocia; a slight increase in the number of malpresentations other than breech is evident, although the data are not separated by parity.

There seems to be little evidence at the present time relating undifferentiated mental retardation to abnormal delivery.

Functional Disorders. In a number of earlier studies, behavioral disorders of childhood were related to history of delivery, but the methods used were crude and do not appear to warrant extended discussion (27, 52, 16, 54). Pasamanick *et al.* (173) compared the pregnancy and labor histories of a group of children with behavior disorders with those of a group of their classmates. The data indicate no appreciably greater frequency of breech delivery or other malpresentations among the patients other than among the comparison group. A somewhat higher frequency of dystocia due to abnormal pelvis occurred among the cases, but the frequency of operative procedures was actually slightly lower among the cases than among the comparison group.

COMPLICATIONS OF PREGNANCY

Since a considerable portion of the evidence linking complications of pregnancy to mental disorders derives from the work of Pasamanick and Lilienfeld and their associates, no attempt will be made in this section of the review to consider the chronic brain syndromes and the other diagnostic groupings

separately. For these authors have stressed the idea of a "continuum of reproductive casualty extending all the way from death to minimum cerebral damage resulting in minor behavioral dysfunction," which might incorporate a number of neuropsychiatric disorders "depending upon the severity, type, or location of the insult" (171, 169, 127, 167). It is consequently difficult to review the work of this group within the arbitrary framework that has been used up to this point.

An identical methodology has been followed in a number of their studies. The method has been to identify from medical care facilities a group of children affected with one of a variety of neuropsychiatric abnormalities—cerebral palsy (127), epilepsy (171, 128), mental retardation (172), behavior disorders (173), speech disorders (168), reading disorders (107), and tics (169). Information was obtained, either from birth certificates, hospital records, or both, as to the frequency of recorded complications of pregnancy or labor. For comparison purposes similar information was abstracted for a group of infants selected from the same series of birth certificates and matched with the patients for race and maternal age and, sometimes, sex and place of delivery. While some elementary data have been presented for specific complications of pregnancy, much of the analysis deals with comparisons of the cases and comparison groups with respect to the frequency of one, two, or more "complications" including conditions as diverse as "non-puerperal complications" and breech presentation. It is clear that the group has in mind a "continuum" of causative agents as well as of end results.

Before reviewing the findings of these studies, it is necessary to express the following reservations about the method:

1. The cases are selected by virtue of attending specific medical care facilities and are consequently unrepresentative of the population of the area with respect to socio-economic status, threshold of illness perception, and so on. On the other hand, the comparison groups are representative of the population except with regard to such variables as have been matched, for

example, race and maternal age. The authors have attempted to solve this problem by comparison of cases and comparison groups with respect to census tract of residence; no appreciable differences have apparently been found. However, while census tract of residence is related to socio-economic status the relationship is not always a strong one. Certain of the disorders studied, for example mental retardation, certainly are related to socio-economic status and the absence of difference between cases and comparison groups in a census tract comparison might as easily be attributed to the weakness of the association between census tract and socio-economic status as to the absence of socio-economic differences between the patient and comparison groups.

2. To be included, a "case" must be both born and resident (at the age of ascertainment) in the area studied, whereas a "control" need only be born there. This inevitably leads to differences between the groups with respect to those factors conducive to family mobility—parity, educational status, etc. The matching by maternal age eliminates this difficulty only partially. Nor is the effect of parity on the frequency of complications considered, although separate examinations of parity associations have been conducted in some instances. This criticism does not apply to the study of behavior disorders (173), in which the comparison group was chosen from the schoolmates of the patients.

3. We have some difficulty with the concept that one can group together in a meaningful way a host of diverse maternal "complications" whose only characteristic in common is their appearance on a birth certificate or hospital record, unless their independent effects have first been examined and shown to be similar. So far as possible, therefore, we have preferred to examine the data with respect to individual complications. Unfortunately, the data are not given in the same detail for the individual complications as for the total number of complications of all types.

These theoretical difficulties notwithstanding, this group of studies constitutes our most valuable body of data on the relationship of complications of pregnancy to mental disorder.

The findings with respect to prematurity and the more obvious difficulties of delivery have already been presented. With respect to those complications that might be thought of as influencing fetal development during pregnancy, the following are the most striking findings:

1. Consistent excess of toxemia during the pregnancies producing the affected children. For children with cerebral palsy, epilepsy, behavior disorders, and speech and reading disorders, toxemia was mentioned approximately twice as frequently as in the comparison series. No appreciable difference between patients and controls is evident in the study of mental retardation.
2. An appreciable excess of placenta previa and other causes of bleeding during late pregnancy (the source of information suggests that most of the bleeding reported would be late in pregnancy) is seen for the cases of cerebral palsy, epilepsy, and reading disorders. This relationship appears doubtful for the children with mental deficiency and behavior disorders.
3. Non-puerperal complications appear more frequently in the children with cerebral palsy, mental retardation, and speech or reading disorders than among the comparison groups. This feature is much less striking in the patients with epilepsy or behavior disorders.

Apart from the studies just reviewed, data on the relationship of abnormalities of pregnancy to mental disorder, or to fetal defect in general, are few. Stevenson (216) found a higher frequency of maladjustment in later life among infants judged to be in poor physical condition at the time of birth than in those judged to be in good condition. However, the proportion of infants thought to be in poor condition was not related to the presence or absence of maternal disease during pregnancy, although it was much higher following abnormal delivery. In a case history study of 105 highly selected mentally retarded children, Stolt noted a frequency of toxemia, other maternal complications, and general stress and anxiety higher than among a variety of, again, highly selected, control groups

(218). Turnbull and Walker, following up 155 women leaving hospital after apparently successful treatment of threatened abortion noted a high frequency of ante partum hemorrhage, due in part at least to a high prevalence of placenta previa, and a higher prevalence of fetal defect than among other booked cases (225). In another follow up study of abnormalities noted during the first twelve weeks of pregnancy, McDonald noted a higher frequency of fetal defect following acute febrile illness and active or quiescent tuberculosis but not following threatened abortion (146). Kunnas, in a very brief report on the follow up of 288 children born of toxemic mothers states that the physical and mental development of the children did not differ from normal, but gives no data (121).

Clearly, here is another area in which new data on a large scale are needed.

Descriptive Epidemiologic Associations

There are many descriptive variables, including order of birth, parental age, family size and season of birth, that are believed to indicate early environmental influence in the etiology of those diseases that are associated with them. However, for inclusion in this part of the symposium it is necessary to demonstrate not only that an etiologic influence is environmental in nature but also that its time of operation is prenatal, or at least perinatal. The time of operation of an etiologic factor can be identified in part by the assumption that it must be prior to manifestation of the disease and in part by consideration of the time period during which the descriptive variable involved can be presumed to differentiate between groups of individuals. Thus, any environmental influence in the etiology of the congenital brain syndromes can be presumed prenatal in action by virtue of the first consideration. However, this consideration alone is of little value in the case of the other two major categories of mental disorder since neither is manifest at birth and may in fact not be observed until many years after birth. Association with month of birth is, therefore, a most valuable observation

in these two categories of illness since, under the second consideration, it seems reasonable to believe that month of birth differentiates between the environment of individuals only during intra-uterine life or during the early months of separate existence. It is very difficult to see, for example, why environmental influences acting later than the first year of life should be related to month of birth. On the other hand, order of birth, parental age, and family size are characteristics that influence a person's environment all the way through childhood until he leaves the parental milieu.

MONTH OF BIRTH

Chronic Brain Syndromes. Significant seasonal variation in the frequency of anencephaly has been reported in British data. McKeown and Record, using vital data from Scotland for the years 1939–1946 noted that the stillbirth rate due to anencephaly was lowest in May (1.91 per 1,000 births) and highest in December (3.09 per 1,000) (148). A similar variation was noted for data from Birmingham, in which information on month of conception was also available. Pregnancies conceived during the half year March to August showed a greater prevalence at the time of birth than did those conceived during the half year September to February. The trend was not due to seasonal variation in the parity distribution of births, although it seemed to be more striking for first births. No seasonal variation was evident in data for stillbirths and infant deaths due to spina bifida or hydrocephaly. These relationships were confirmed in later data by Edwards (64), who found no substantial difference between the first born and later born anencephalics in the extent of the seasonal variation.

The largest series of malformations of the central nervous system so far examined in this country, including 326 cases of anencephaly, did not show any seasonal variation for any of the three major diagnostic categories (137). The possibility that the seasonal trend noted in British data is absent in this country requires confirmation. If it is confirmed it is indicative of

a most interesting difference between the two countries in the epidemiologic characteristics of anencephaly.

Three small series of cerebral palsy children, totaling only 339 cases, have been reported from the point of view of month of birth (23, 125, 212) with no consistent trend evident. However, no large series appears to have been examined from this aspect.

Mental Retardation. The relationship between season of birth and intelligence quotient has received a good deal of attention. In 1943, Pintner and Forlano (182) reviewed studies reported prior to that time, including their own extensive studies of school children in New York City (179, 180, 183) and in the Southern Hemisphere (181) and other very large scale studies of school children (26, 84, 74), college students (92, 150, 76, 38), and other adults (73). Among sixteen groups studied, there were ten in which the lowest average intelligence quotients were for persons born in winter[1] and four in which the lowest I.Q.'s were for persons born in autumn. One of the two exceptions to this pattern was the smallest study reported, based on only 337 cases (134). The other was a small but carefully planned Scottish study in which four approximately equal samples of children born on the first days of February, May, August, and November were examined (139). Pintner and Forlano report the results of this study as an exception to the general pattern. However, two separate reports of this study (139, 196) list the average I.Q. for the February-born children as 99.6 and 96.6, respectively, presumably because of a misprint in one of the reports. If the latter figure were in fact the correct one, the February-born would have the lowest average I.Q. of the four groups of children and the results would be consistent with the majority pattern.

Subsequent to 1943, Roberts (190) has published a study based on all children in the town of Bath born during a four-year period, the results of which are generally consistent with

[1] December through February in the Northern Hemisphere studies, June through August in the Southern Hemisphere.

the above except for being stated in terms of month of conception rather than of birth. The results of a rather small study of prison inmates by Corsini (46) were not consistent with previous findings, highest average I.Q.'s being found for winter-born and fall-born prisoners.

The relationship between season of birth and intellect has also been studied by examination of the season of birth of mentally retarded children. Blonsky (26) and Pintner and Forlano (181) report an excess of births of mentally retarded children in the winter months, observations that are generally consistent with the general observation of low average I.Q.'s for children born in the winter months. Nolting (162) presents data on approximately 13,000 Dutch and 7,000 British mentally retarded children. In both series there is an excess of births in the months of June and July and a deficiency of births during the period October through January. This finding is not consistent with those of the studies reviewed by Pintner and Forlano. However, the statistical methods used in the various corrections that are applied by Nolting are not clear to us. Furthermore, the data are presented in such a manner and with such an obvious desire to substantiate an hypothesis that we are reluctant to accept these findings as indicative of a difference between American and European experience without independent conformation of the finding in the European data.

Without doubt the most challenging recent observations in this area have been those of Knobloch and Pasamanick (115) who examined the months of birth of children admitted to a school for the mentally retarded over the 36-year period 1913–1948. By comparison with seasonal birth rates in the same State a form of relative risk of first admission was derived according to month of birth. Relative risk was highest for children born in February (1.507 per 1,000) and lowest for those born in August (1.297 per 1,000). This trend is entirely consistent with the studies of I.Q. reviewed by Pintner and Forlano. Furthermore, Knobloch and Pasamanick noted that there was a varia-

tion in risk of admission from year to year, which they related to average temperature during the summer months. Believing that the eighth to twelfth weeks of gestation are critical ones in the development of the intellect they noted that this period would fall in July for the group of children born in February who showed the highest admission rates. Admission rates for those born in January, February, and March, respectively, were therefore compared for the years following the years in which the temperatures in June, July, and August, respectively, were above and below the median. When the eighth to twelfth weeks of gestation fell in June there was no significant difference in risk of admission between years with temperatures above and below the median. However, when the eighth to twelfth weeks fell in July or August the relative admission risks were 1.658 and 1.519, respectively, when the temperature was above the median compared to 1.276 and 1.206, respectively, in those years when the temperature was below the median. The differences were highly significant and the relationship was consistent in different time periods.

These observations are, in our opinion, among the most significant recent observations in this general area. Their potential significance seems to demand attempts at confirmation in other geographic areas. While the number of cases involved in this particular study is large, the compilation of even larger numbers would enable additional examinations, such as the use of a finer breakdown of temperature range rather than the simple dichotomy used, and more detailed examination of the relationship in different time periods. It would also be desirable to examine the relationship of admission rates to temperature fluctuations during other months than the three chosen, since it is not clear why the eighth to twelfth weeks of gestation should be assumed to be the only ones critical to intellectual development.

Although much more work could be done in exploration of the relationship of I.Q. to season of birth, a review of the work already to hand leaves the distinct impression that a real relationship exists and exhibits a fair degree of consistency from

time to time and from place to place. In explanation, the following possibilities have been offered:

1. Selective seasonal reproduction in relation to intelligence of parents. This possibility was suggested by Goodenough (83) on the basis of observation of a seasonal trend in birth rates for families in the higher occupational classifications and absence of such a trend in the lower occupational groups. The data are not presented in detail and are consequently difficult to evaluate. The possibility is supported in a more satisfactory method by Roberts (190) who noted that:

> The seasonal variation in I.Q. noted for a cross-section of children was in one sample virtually eliminated and in another sample actually reversed when examination was restricted to children of the same parents conceived at different seasons, and
>
> The children conceived in winter (whose average I.Q. was highest) had appreciably and significantly fewer siblings than did those conceived in summer.

It is difficult to see why the more intelligent parents should plan to have their children during the hottest months of the year, but nevertheless the arguments offered by Roberts have not been satisfactorily answered. A relationship between season of birth and intelligence of parents may not necessarily be the result of conscious planning. In view of the well-substantiated relationship between sibship size and I.Q., Robert's observation of a lower average sibship size for winter-born children could alone explain the relationship between I.Q. and season of birth. It might also be noted that the absence of a seasonal relationship of birth rate with socio-economic status does not presuppose a similar situation with respect to intelligence of parents.

2. Selective seasonal reproduction related to socio-economic status, the relationship between risk of admission for mental retardation and socio-economic status being generally inverse. This possibility was dismissed by Knobloch and Pasamanick

(115) on the basis of an examination of the month of occurrence of 23,000 births in Baltimore, which is said to have indicated little evidence of differences between socio-economic classes (determined by census tract of residence) in the seasonal distribution of births.

3. Seasonal variation in the parity distribution of births appears not to have been considered by any of these groups of workers. There is a remarkable paucity of vital data on the relationship of season of birth to parity. However, the fact that certain congenital malformations (anencephaly in this country and spina bifida in both this country and in Britain) show strong relationships to parity and yet do not show seasonal variation in frequency suggests that the relationship between parity and season of birth is not sufficiently strong to produce indirect seasonal associations in mental retardation.

4. Temperature effects during critical periods of intra-uterine development. While the direct effects of temperature on mental ability are undoubted (*see*, for example, Mills) (151, 152), it is difficult to see how temperature variation of the order associated with seasonal fluctuation could be responsible for permanent brain damage (particularly that occurring prenatally) except as temperature variation may itself influence other factors such as nutrition or infection.

5. Variation in maternal nutrition associated with variation in environmental temperature during periods of critical intra-uterine development is the explanation favored by Knobloch and Pasamanick for both the seasonal and year-to-year variation noted in their study. A quite specific nutritional factor (maternal Vitamin C deficiency) has been implicated by Nolting. Nolting shows a remarkably high correlation between seasonal variation in maternal Vitamin C levels and his own data on mental retardation, but, as noted, the statistical methods used are unclear and the data on mental retardation are not consistent with data from this country. It seems premature to implicate a specific nutritional deficiency at this time, although the general area of hypothesis is attractive.

Other possible explanations include seasonal variation in maternal complications of pregnancy, such as those noted by

Pasamanick and Knobloch (170), and possible relationship of intellectual development to infections during the early months of life.

Functional Disorders. Tramer (223) noted that among 3,100 patients admitted to a Swiss mental hospital during a 52-year time period there was a relative excess of those born in the months December through March compared to what was believed to be the general seasonal distribution of births. A similar situation has been found by Nolting (161) in an examination of the birth dates of 2,589 schizophrenic patients. The latter also claims to have noted a seasonal variation in the birth dates of 3,000 male psychopaths (162), although the pattern of the variation is not described. These results would seem to require confirmation, and, in view of the simplicity of the information required, it is surprising that more data have not been presented on this subject.

BIRTH ORDER AND MATERNAL AGE

Associations with birth order or maternal age are of significance in that: (1) they indicate the existence of environmental etiologic factors, and (2) they may assist in the identification of such factors. Associations of disease incidence with one or other of these variables rarely have practical implications *per se.* Consequently, the less that is known about the etiology of a disease, the more important knowledge of such an association becomes. In the context of this review, associations with birth order and maternal age seem most significant in the case of (a) congenitally manifest conditions (since it can be assumed that any environmental influence in such conditions is prenatal in origin), and (b) conditions whose etiology is obscure. The congenital malformations fit these criteria most closely. Birth order or maternal age associations for those chronic brain syndromes that originate in the perinatal period, e.g., cerebral palsy and epilepsy, seem of less significance than for those originating early in pregnancy, since a number of recognized etiologic factors in the former group of defects might well be

expected to be associated with order of birth and maternal age —for example, jaundice, trauma, asphyxia.

In the case of the functional disorders, and to a lesser extent in the case of mental retardation, associations with order of birth or maternal age may well be of considerable interest, but one can have little assurance that the environmental influences they reveal are prenatal in origin. The functional disorders will not, therefore, be included in this section of this review.

Chronic Brain Syndromes. The congenital syndromes that include a "mental" component and that have been demonstrated to have associations with order of birth or maternal age are mongolism, anencephaly, and hydrocephaly.

The association of mongolism with age of mother is so striking that it became evident at least fifty years ago as the result of clinical observation (206). In spite of the inadequacy of many of the comparison groups used and the variety of the sources of data, subsequent studies have invariably confirmed the presence of this association (101, 194, 122, 24, 19, 13, 69). In one of the few studies in which a series of mongol children can be related directly to the population at risk, Carter and MacCarthy (36) noted a consistent increase in prevalence with increasing maternal age from zero in the children of mothers under 20 and 0.29 per 1,000 in the age groups 20–29, to 26 per 1,000 in the children of mothers aged 45 or more. Early writers also commented frequently on the tendency of mongols to occur at the end of large families. However, Penrose (174) showed that this apparent association with birth order results from the association of mongolism with maternal age and the close correlation between birth order and maternal age. In fact, it has been shown recently that, if maternal age is held constant, there is a slightly higher risk of mongolism in the first born compared to second and later born (164, 210).

Penrose (176) examined a small series of cases of malformations of the central nervous system by the Greenwood-Yule method and found increasing risk with increasing maternal age and birth order; maternal age seemed to have the closer asso-

ciation. In a much larger series, Record and McKeown (189) assembled sufficient material for adequate examination of the separate diagnoses and also obtained information on the birth rank and maternal age distribution of the related population. Prevalence of anencephalus and spina bifida was found to be higher in first births and in births after the sixth than in the intermediate birth orders. No association with maternal age was evident for these two malformations when the influence of birth order was held constant. On the other hand, hydrocephalus showed increasing prevalence with maternal age, and little independent effect of birth order. Generally similar findings have been reported in examinations of data for stillbirths in Scotland (189, 138, 64), except that it is not possible to examine the effects of the two variables independently in these data and the pattern of birth order association for anencephalus suggests a gradual increase in risk with birth order (after the initial drop from first to second births), rather than the low plateau between second and sixth births suggested by the Birmingham data.

There seems to be some variation in these patterns from place to place and time to time. Thus, a small series of anencephalics reported from Ireland indicated a higher frequency in the children of mothers over 30 years of age but no significant independent effect of birth order (39). In a study of children born with malformations of the central nervous system in Rhode Island between 1936 and 1952, the general patterns were similar to those noted by Record and McKeown, but the difference in risk of anencephaly between first and second births was generally smaller than that noted in Birmingham and in the latest time period examined (1948–1952) was non-existent (99).

In our present state of knowledge it does not seem profitable to speculate on the interpretation of these associations, beyond noting broad categories of variables that may be related to birth order and/or maternal age. These include a variety of social and economic circumstances, changes in maternal anatomical and physiologic characteristics, and frequency of maternal dis-

ease. It should be stressed that these associations have been demonstrated in prevalence, not incidence, data, and are susceptible to variation not only through changes in incidence (occurrence of the disease) but also through changes in duration (i.e., differences in the survival of affected and not affected children).

Associations of epilepsy and cerebral palsy with birth order and maternal age have been studied by Beall and Stanton (14), Yannet (246), and Lilienfeld and Parkhurst (127), among others. The latter authors have pointed out that the patterns of association are similar to those that have been found for perinatal mortality, for example by Yerushalmy *et al.* (250). This similarity forms part of the basis of their concept of a "continuum" of fetal damage.

Mental Retardation. The results of examination of the birth rank distribution of series of mental defectives have not been consistent. Thus, Dayton (51), in data on 10,455 retarded Massachusetts children found no association with maternal age, and no association with birth order when the evident effect of family size was held constant. Turner and Penrose (226) suggested that the relationship might vary with the severity of the defect—"low-grade" deficiency being a characteristic of the first-born and "high-grade" deficiency occurring more frequently in the higher birth orders. Malzberg (140) found a higher than expected proportion of first born, but not the excess in the later birth ranks noted by Turner and Penrose. Most recently, Lilienfeld and Pasamanick (130) found a striking increase in frequency with increasing birth rank which was present in each maternal age group; an association with maternal age was also present but was not clear cut when parity was held constant. No account was taken by these workers of the association between family size and mental defect.

The relationship between family size and intelligence quotient is a strong one, and must be considered in studying the relationship of I.Q. in "normal" children to birth order and parental age. This may be done by comparing individual family

sizes (147) or, more satisfactorily, by comparing sibship pairs and other combinations from the same families. When the latter method has been followed, some early studies suggested that average I.Q. is higher for the later born than for the first born (7, 45), but in later studies no significant effects of maternal age or birth order have been demonstrated (105, 95, 191).

OTHER DESCRIPTIVE CHARACTERISTICS

Mention should be made of two other characteristics of the epidemiology of anencephalus that strongly suggest the existence of important environmental determinants of an unknown nature. One of these is the striking secular change in prevalence. Both in England and Wales (138) and in Rhode Island (137) the frequency of this malformation was almost half as high in the years around 1950 than it had been in the early war years. Such changes cannot be explained by any genetic mechanism. Secondly, the marked relationship of anencephaly to social class noted by Edwards (64) is strong evidence of environmental etiology.

Conclusions

Direct evidence of damage due to fetus-environment interaction exists with respect to the chronic brain syndromes that originate in the perinatal period. The nature of the environmental agents that are productive of brain syndromes during the early months of pregnancy is to a large extent unknown, although there is indirect evidence that they exist and some few rare toxic agents have been identified. Evidence that the functional disorders may be related to prenatal damage is yet to be found.

A great deal of descriptive (i.e., survey) work remains to be done in the field of congenital malformations to formulate hypotheses applicable to man. A vast amount of experimental work in this area has been of value from the point of view of biologic understanding but has not produced a single hypothesis capable of substantiation in human data.

In the field of perinatal brain syndromes the type of research

most lacking appears to be the identification of the possible minor effects of lower exposures to agents whose major effects are well documented. Such research requires carefully planned and documented observation of cohorts of exposed individuals. Such studies must be large and will necessarily be expensive, but no alternative method of securing this type of information is available.

In the area of mental retardation a number of challenging hypotheses linking mental defect to general environmental circumstances during the early months of pregnancy await test. In addition to direct tests of, for example, the influence of temperature and/or maternal nutrition, further descriptive studies would appear to be indicated in order to test the generalizability of the observations on which the hypotheses are based.

In a search for evidence that the functional disorders might be influenced by prenatal circumstances, it would seem desirable to check thoroughly those observations that link functional disorders to characteristics evident at birth. The possibility that functional disorders may be related to month of birth or birth weight are facts that have a theoretical significance far deeper than that which is immediately apparent.

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Discussion

Dr. Paul M. Densen: I am really very awed by the amount of work that must have gone into this kind of a review and grateful for the opportunity to go over it.

I have taken the purpose of my assignment from Dr. Boudreau's letter asking me to attend this meeting, in which he said that the function of the discussant was to raise issues that the paper suggests in the field generally, and, possibly if we had the time and interest, we might take up a few items of special interest to the discussant.

Consequently, I consider my role to be more or less that of a catalyst, to try to get you talking about the paper rather than to do most of the talking myself.

I have approached the problem of reviewing this paper on the assumption that the kinds of evidence that are needed in this field are just the same kinds of evidence that are needed in any other field, but that the order of probabilities may be very different in the mental health field than you have in some of the physical sciences.

Since the field of mental health is one with which I am not too well acquainted, I tried the usual trick of going back to something with which I was a little bit more familiar.

There were two main points that struck me in reading over Dr. MacMahon's review. One of them is a basic question which, it seems to me, applies to Dr. Böök's paper as well as Dr. MacMahon's and perhaps to many of the other papers in our symposium. This is related to this kind of question:

When you psychiatrists say: "This is a schizophrenic individual and that one is an individual with psychosis of one kind or another, and this is a case of functional disorder of one kind or another," what is the probability that another physician—another psychiatrist

—looking at these same individuals is going to say that this individual is a schizophrenic, etc.?

In other words, how reliable do you think your diagnoses are in this field, and have there been any studies of this? I think this is a rather basic problem.

This is not to say that you necessarily are going to have orders of probability that are like .99 or anything of the kind, but I think it is important to know something about where the variation exists among different individuals in making these kinds of diagnoses and what kind of things they tend to vary on.

I wonder whether there have been any studies of this kind in the field. I am reminded here very much of the kind of thing that has happened in tuberculosis, in some of the reports of Yerushalmy and Birkelo when they studied the problems of reading x-rays and the kind of things they turned up. Their findings were a little shocking to some of the clinicians in the field, and I think that you have somewhat the same problem at the present time, for it is a problem that will always be with us in the diagnostic area.

The second major issue that occurred to me, as I read through this paper, seemed to be the question of integration—or interplay—between observations which are made on the population, and observations which are made in the laboratory and by the clinician.

I will try to indicate what I mean by writing this, shall we call it, chemical equation. The arrow indicates reversible reactions,

$$\left.\begin{matrix}\text{Population}\\ \text{Observations}\end{matrix}\right] \longleftrightarrow \left[\begin{matrix}\text{Clinical and Laboratory}\\ \text{Observations}\end{matrix}\right.$$

We have "Clinical and Laboratory Observations" on the one side, and we have "Population Observations" on the other side. If you like, we can put the sociological type of observation on the side of the population, and perhaps we might want to make it a three-way equation, but we will probably be talking more about that in some of the later papers. As the equation shows, these are interrelated-type of observations. However, I wonder whether we have really looked at the mental health problem from this standpoint of a "reversible" reaction.

Let me see if I can illustrate what I mean quickly with the example of pellagra. For example, if I remember my school days well

enough, when Goldberger and Sydenstrycker were studying pellagra, they first got the idea that it had something to do with nutrition from clinical and laboratory observations. They noticed in the clinical situation that most of these cases were poor, rural individuals. They also had certain kinds of laboratory evidence that suggested that possibly some nutritional factor was involved but this was just a hunch or hypothesis at this point.

This led them out into the population, particularly Goldberger, and here they were able to pin down the idea that something in the diet had something to do with the development of pellagra. Obviously there were social factors involved in this, also.

The interesting thing to me is that they didn't stop there. They came back into the laboratory after the population observations and began to see if they could isolate the particular factor in the diet that was involved as one of the agents in the development of pellagra. I don't remember well enough whether they actually isolated the B complex and niacin or just what they did, but I do remember that they were able to identify some elements in the diet that were responsible for the development of pellagra.

You can make this same argument for cholera, although taking it back into the laboratory and the identification of the cholera organism took place quite a bit later in time.

Now I would like to take this kind of an approach over into the mental health field and see if I can make the connection. Let us take the question of prematurity. This is a particular kind of agent which Dr. MacMahon has mentioned and which occupies a good portion of his paper.

If one were able to rank the various agents in order of importance relative to the frequency of mental disorders associated with them, I think prematurity would probably head the list.

About 6 per cent of the single births in the United States are premature. We know very little about the causes of prematurity. There is, in the literature in this field, as far as I am aware (and you, of course, are more aware of this than I), very little detailed description of the physiological and biochemical dynamics of pregnancy—what happens to the biochemical structure of this woman as she goes through pregnancy.

There seems to be very little information about the changes that take place during the course of pregnancy, and there is still less in-

formation in the literature relating the various patterns which presumably exist to the occurrence of prematurity.

This is just a long-winded way of saying what your medical student said about there being very little information available.

As I got to thinking about this I wondered whether this is due to lack of interest among obstetricians about this, so I started to look around the members of the group here. As far as I am aware, there are no obstetricians in our group. And while I didn't take the trouble to go through a medical directory to see how many authors were obstetricians amongst all the references that you gave, I did get the general impression that there weren't a great many of them. The one outstanding individual in this area seems to be Dr. Eastman at Johns Hopkins, but he seems to be the exception rather than rule.

It was rather interesting to me that Dr. Böök had already spoken of the need for finding physical or biochemical correlates, and I again refer to the need for an interplay between these two sides of this so-called chemical equation.

I have the feeling when I read this sort of material that what has happened is that one side of this equation—the right-hand side—has been examined in more or less detail; this is the part that Dr. MacMahon has reviewed. But so far there is relatively little on the left-hand side of the equation; or if there is such information available, we haven't yet linked it up with the right-hand side.

In my concept of epidemiology, one does not have a complete epidemiological picture until one sees the relationship between the two sides of the equation. I am sometimes a little concerned to find people only meaning the right-hand side of the equation when they use the term "epidemiology." If we go back to classical epidemiology, we will find that the epidemiologists we hold up as the fathers of the discipline did not think of the term as involving only one side of this equation.

Dr. MacMahon suggests that we should develop further a large number of cohort studies in this area. Usually these studies, like those of Dr. Pasamanick and others, start with the premature baby and follow this baby forward. Relatively little seems to be known about their mothers, yet we know from the studies of Yerushalmy and others that the mothers who have premature babies or complications of pregnancy are those who have had similar difficulties in previous pregnancies. This is a fairly well demonstrated fact.

Can we make use of this observation to try to further characterize these women physiologically and biochemically?

One of the questions that occurred to me to wonder about, was the mental health history of all of the offspring of these mothers who have premature babies or who have had complications of pregnancy as compared with controls.

So far as I am aware, the usual thing that is done is to take the current pregnancy and compare it with a control. But wouldn't we add to the strength of the evidence if we took the whole picture, recognizing the fact that these mothers are somehow a selected group? Something must happen to these mothers which makes them much more likely to have a subsequent premature baby or a complication of pregnancy.

In this regard, the studies of the National Institute of Neurological Diseases and Blindness, which I imagine most of you are familiar with, should provide considerable data on the mother because, as you know, they are taking very detailed observations during the course of pregnancy on mothers who come to medical centers all over the country.

This raises another issue. I don't know what kind of an issue this is, or how one would classify this issue—whether one would call it administrative, financial or logical or what—but I will describe it to you and you can worry about its classification.

Is it only possible to obtain the kind of information we are talking about from such multimillion dollar studies as the National Institute of Neurological Diseases and Blindness study on selected populations? If that is so, then we are in an awkward kind of position. But I hardly think this is the only approach.

The NINDB study uses a shotgun approach to this problem, and perhaps this is necessary at this stage. However, I wondered in reading over Dr. MacMahon's review, whether any of the data now available, were they to be examined in the light of present biochemical and physiological knowledge, would permit the formulation of more specific hypotheses which could be tested without raising the limit on the national debt?

Is it possible to write a review, one like Dr. MacMahon's but which is concerned with the left-hand side of the equation, and then try to put both sides together, or don't we have any observations on the left-hand side of that equation?

Dr. MacMahon's review impressed me with the need for better appreciation of the requirements for research and for some uniform way of communicating results in this field.

For example, Dr. MacMahon makes the statement, "Eastman and DeLeon, in one of the few controlled studies, studied 96 children with cerebral palsy with 11,195 surviving normal children. These data would suggest an incidence of cerebral palsy 40 times higher in those who did not breathe for six minutes or more than in those who breathed within six minutes."[1]

The thing that interested me here is the notation that it was "one of the few controlled studies. . . ." As one goes through this material one finds over and over again that one is tempted to make this kind of a statement. This is disturbing to a statistician.

This lack of controls, of proper design of the experiment, is a problem common to many of these areas. What can be done about it?

While perhaps I should take a fatalistic point of view and say, "Well, as time goes on these things tend to iron themselves out," I just wonder whether there is any way of hurrying the process up.

It concerns me that in this field—which is such a difficult field anyway because of the problems of diagnosis that I mentioned earlier and the general difficulty of defining the things that one is measuring—that adequate research designs seem to be so often lacking.

The other area I want to speak of is the reporting of results. I had the experience recently of sitting in on Dr. James' Subcommittee on Primary Prevention in Mental Health of the American Public Health Association, and trying to get some notion of what the incidence rates were for the various types of mental disorders. By ranking them, the public health administrator could get some notion of what problems he might want to concentrate on first. I found it a very frustrating experience because one person would say: "Of the total number of cases of German measles, such-and-such a number of the children developed some kind of mental defect." While the next would say: "Of the cases of children with mental defects, a certain proportion of them had previously had mothers who had German measles." But one cannot put the two statements together, and as one reads through the literature it gets more and more frustrating. Lest I wind up a mental health problem myself, I quit reading it and decided to bring the problem to you, hoping that perhaps you could suggest some

[1] P. 31.

way of developing a little more uniformity into the way in which results are presented so that they can be compared.

The final thing I want to speak of takes advantage of Dr. Boudreau's suggestion that we might harp on some particular aspect which might be of specific interest to us individually. This has to do with the last section of Dr. MacMahon's paper in which he takes up the kind of population observations that have been made, such as relationship between the season of birth, certain kinds of measurements of intelligence, and so on.

One of the things Dr. MacMahon speaks of is the relationship of birth order with chronic brain syndromes that originate in the perinatal period, for example, epilepsy. There is also discussion on the influence of maternal age.

The thing that struck me as being rather interesting and curious is that some of these things are correlated with birth order but not with age, and, conversely, when birth order is held constant, some of these things vary with age of the mother.

If one holds the age of the mother constant, and one finds something varying with birth order, then something seems to happen to this woman from one pregnancy to the next. What is this thing? What is happening to this woman?

Conversely, if one holds the birth order constant and something varies with age, presumably there is some physiological correlate with the aging process—possibly this is an environmental factor that operates. But what is this thing that varies with age, yet doesn't seem to vary with birth order?

As I got to be curious it led me around in a circle to where I first started, namely, what is known about the biochemical and physiological changes in pregnant and non-pregnant females with age? And how does this relate to the kind of observation which Dr. MacMahon has made in his paper?

These are some of the thoughts that occurred to me. The only observation I really have to make is to wonder how one can fill in the equation that I set up on the blackboard.

SUMMARY OF DISCUSSION

1. Dr. Rosen expanding on Dr. Densen's remarks, asked about the changes which take place in women as they age that can affect the

course of a pregnancy. He pointed to two approaches which have not been pursued in great detail.

One approach is to ask, What actually happens in the placenta and in placentation in the older woman? The role of placentation might well be a point of departure for future studies. The other approach is to study the relation of parity to the immunochemistry of the mother. For example, are antibodies produced increasingly as the number of pregnancies increases and, if so, which ones? While this question has been studied it has not been studied specifically in relation to parity. These are two areas where research might prove to be useful.

However, when an association is found between parity and some condition of the offspring, it is necessary to interpret it with caution. There seems little doubt that some of these parity associations result from physiologic changes in the woman, yet it should not be assumed that something necessarily happened to change the same woman from one pregnancy to the next. Because, in the aggregate, the class of women having their first child, and the class of women having their sixth child, are composed of two quite different kinds of women. Undoubtedly selectivity is at work. There are characteristics that tend to place women at different levels of parity; and it might be that it was some of these characteristics rather than parity itself that brought about an observed association with some condition in the offspring.

2. Dr. Pasamanick asserted that it was not enough to give attention to each factor as a separate variable. More reference was needed to the interaction among variables. As an instance, when Dr. MacMahon discussed natal events he ignored to some extent the interrelationship of these with prenatal events.

Thus natal difficulties such as apnea and cyanosis in the infant showed a very high association with complications of pregnancy. It might very well be that prenatal damage in the brain respiratory centers of the fetus accounted for natal respiratory difficulties. In fact, there was evidence from pathological examinations which showed that it was either the premature infant or the infant who was subjected to some complication of pregnancy, who was chiefly affected by anoxic damage.

3. Another interrelationship that he mentioned was the high inverse association of socio-economic status with complications of preg-

nancy and prematurity. This relationship was worth examining for two reasons. It might provide clues to etiology, and it was undoubtedly complicating and confounding the import of many social and cultural variables.

A number of specific comments were offered by Dr. Pasamanick that stemmed from the studies that he and his associates had done.

4. Very little relationship was found between obstetric complications and neuropsychiatric disorders in the offspring. But this investigation, like others of its kind, was done in cities where obstetrical care was relatively good. Perhaps elsewhere difficulties in labor and surgical procedures might be found to play a more important role; although the evidence for suspecting it was not strong.

5. Some of the reservations expressed by Dr. MacMahon about the methodolgy used in a number of Dr. Pasamanick's studies on the complications of pregnancy were weli taken. However, Dr. MacMahon's point about bias with regard to socio-economic status in the experimental and control samples (pp. 44–45) needed clarification: Bias might operate either for or against the hypothesis under test, though perhaps more heavily against it. The reasoning was that if those who were socio-economically retarded were removed from the experimental group, the differences between cases and controls would be even greater. Possible evidence for this supposition was derived by analyzing the dependent variables by I.Q. in the Negro group.

6. As to the question of socio-economic differences in the distribution of births by season, there existed very definite evidence based upon data covering five years of births in Baltimore. The seasonal distribution of births in the upper economic groups showed extremely little variation, while the lower economic groups, both Negro and white, showed a large decrease in births during the winter. This finding was important to any hypothesis that related seasonal variation in the birth of mental defectives to seasonal variation in the over-all birth rate: it would seem necessary to control for social class to avoid bias.

7. On the basis of all births in the United States during 1955, it was found that there was a significantly lower birth weight in summertime. This fact may be attributed, in accord with an entire chain of evidence, to decreased nutritional intake in summertime, considering that the fetus takes on weight largely in the last trimester.

8. No relationship at all was found between the births of mentally defective children and the 1918–1919 'flu epidemic. This finding was not discussed in Dr. Pasamanick's paper on seasonal variation, although the possibility of such a relationship was the original reason for taking it up later. Possibly, if the finding had been made known, the subsequent studies on Asian 'flu might not have been considered necessary. In any case, it seems a fact that 'flu does not have any prenatal effect.

9. On the relationship of season of birth to schizophrenia, most studies in the literature reported that more schizophrenics were born in wintertime. But this finding was not confirmed by a study of all admissions to the Columbus State Hospital over a sixty-year period.

10. However, temperature variation (which had been found related to mental retardation) *was* found related to schizophrenia. There was a very significantly higher rate of schizophrenia in individuals born after hot summers than after cool summers. At present, the only hypothesis that was advanced was that a hot summer might produce enough prenatal damage to act as a precipitating factor.

Dr. MacMahon: It is important to distinguish two general types of explanation of associations of fetal characteristics with birth order. The first, and more obvious, relates to maternal physiologic or pathologic changes that proceed in association with childbirth. Associations having explanations of this type would be apparent in comparisons of the same mothers at different birth orders. The second type of explanation derives from the fact that in a cross section of births in a population, different social, ethnic and other cultural classes are represented in differing proportions in the various maternal age and parity groups. It seems likely that both these types of explanation are pertinent to birth order associations in the mental disorders; having noted a birth order association, we cannot jump to one conclusion or the other.

Dr. Pasamanick's point (Point 2) concerning the identification of causative complexes as distinct from single variables is an important and difficult one. Certainly, although epidemiologic research generally proceeds by the identification of one or two factors at a time, preventive measures frequently involve alteration of broad complexes such as "cleanliness" of food and water, or "quality" of obstetric care.

As stated in our review, we have been unable to find convincing evidence of prenatal influence in the psychoses or neuroses. Dr. Pasamanick's observation of the effect of temperature during intrauterine life on incidence of schizophrenia is therefore particularly interesting (Point 10). It seems strange, however, that temperature variations of the order noted for the same season between years could have an influence, while variation between seasons within years does not.

THE EPIDEMIOLOGY OF MENTAL DISORDER ASSOCIATED WITH DAMAGE TO THE BRAIN AFTER BIRTH

GEORGE JAMES, M.D.

IN our current stage of knowledge and ignorance of the etiology of mental disease, those factors which are known to be associated with brain damage offer a fruitful field for epidemiologic study. While good evidence exists that such damage can cause behavioral disorders, there is still great need for clear cut explanations of the relationships between the cerebral pathology, its presumed etiologic background and its dependence upon a number of ill-defined associated factors. The voluminous literature on the subject offers some facts and many hypotheses, but few complete pictures. There is a great need for well-planned, well-controlled, incidence-measuring, prospective studies. This present summary will discuss a few of the most promising leads under the general titles of jaundice, anoxia, trauma, poisons, infections, deficiency diseases, convulsive disorders and cerebrovascular disease. It will be concerned essentially with those conditions which produce permanent brain damage as distinct from those associated with an acute and reversible disorder not resulting in chronic cerebral pathology.

JAUNDICE

Although it is believed that one per cent of institutionalized mental defectives suffer from kernicterus (31) the exact cause of high serum bilirubin in each specific case is not known. Two mechanisms appear to be of significance—the blood group incompatibility between mother and fetus which leads to continued red cell destruction after birth (39) and the immaturity of the liver of some neonates which prevent the proper conjugation and detoxification of the indirect acting bilirubin to the non-toxic, direct acting form (34). It is known that the proximate cause of kernicterus is the high level of serum indirect

acting bilirubin which is dangerous at levels over 30 mg. per cent and possibly hazardous at levels over 20 mg. per cent (13). Since bilirubin levels can rise rapidly during the first days of life with immediate signs of kernicterus, any level approaching 18 should lead to careful observation of the patient and preparation for exchange transfusion. Although it possesses its own case fatality risk, exchange transfusion is still the treatment of choice and should be performed one or more times as required to reduce serum bilirubin promptly to safe levels. Simple transfusion can add to the hazard by increasing bilirubin levels. Early signs of kernicterus can be reversible, the brain damage appearing to be a product of the bilirubin concentration and length of brain exposure to this concentration.

Since hyperbilirubinemia tends to be more common in the premature infant, it is often difficult to rule out the significance of a number of other factors in a resultant mental deficiency. The premature has a greater risk of having cerebral agenesis, birth injury, anoxia and prenatal infections. He is more apt to have received injections of vitamin K, which some believe can itself contribute to higher serum bilirubin levels, although in one carefully studied series the administration of vitamin K appeared to have had only a minor effect (34). Nevertheless, the liver of the premature is known to be deficient in its ability to detoxify bilirubin and it is probable that this mechanism alone can lead to the brain damage responsible for mental disease. Some suggest that the administration of glucuronic acid may aid in the conjugation and detoxification process and reduce serum bilirubin levels, but this procedure is still experimental and not without danger. Finally it should be noted that the antibody coated red cells of an erythroblastotic child are grossly deficient in oxygen carrying capacity and the resultant anoxemia may itself be a possible contributory cause of the brain damage (1).

A longitudinal study of the effects of a wide range of serum bilirubin levels is now being undertaken by Day and associates. Early findings suggest some measurable effect on growth and

development of the infant exposed to concentrations of bilirubin below the level of kernicterus toxicity (20).

Anoxia, Anoxemia, Ischemia

The newborn possesses both the greatest exposure to the hazard of asphyxia and the greatest resistance to its effects. Anoxia can cause the death of the infant but it is not known whether the survivors have a degree of brain damage sufficient to affect mental function. Darke (9) noted a 12 point lower than normal average I.Q. among children age 2 to 11 who suffered severe asphyxia at birth. Keith and Norval, on the other hand (22), found that survival meant no significant brain damage at least during the first few years of life, during which period they performed their observations. There is obviously a need for more extensive and prolonged longitudinal studies to supply definitive answers to this question. While the general lowering of the metabolism during periods of anoxia may protect the infant from the effects of inadequate oxygen, these secondary changes may in themselves be related to brain damage. From animal experimentation as well as some human studies, one must accept for the present that anoxia is a possible contributing cause of mental disease, although it can not be shown to be a major cause.

The epidemiology of anoxia and anoxemia is itself worthy of more intensive study. Birth injury, drugs given the mother for sedation, analgesia and anesthesia, prenatal hypoxia with contributory effects of the oxytocic drugs, infant infection, and congenital anomalies can each play a role. The exact importance of each is not well defined.

Brown (7) points out that while the infant is quite resistant to the CNS effects of anoxemia he is no better able to withstand ischemia than the adult. He believes that much of the cerebral pathology blamed on anoxemia is in reality due to the persistence of inadequate circulatory pathways after birth. Cardiac shunts, deficiencies in pulmonary circulation, neonatal shock, subnormal concentrations of pressor amines, may all lead to a

lowered cerebral blood supply. Hyaline membrane, a cause of anoxemia once believed due to the aspiration of amniotic fluid, now appears to be more closely related to improper circulatory mechanics, maternal diabetes, and disturbances of body water concentration. As Brown has stated, whatever its primary cause, recovery from hyaline membrane disease depends upon normal pulmonary flow, systemic pressure and cardiac output.

Anoxia and asphyxia in the adult are caused by nitrous oxide, drowning, carbon monoxide, or mechanical suffocation and can result in permanent brain damage in those who recover. Fletcher (12) has noted eight examples of permanent personality degeneration following nitrous oxide anesthesia. Similarly, after an unsuccessful attempt to commit suicide by hanging, the patient will suffer choreo-athetotic hyperkenesis, epileptic fits, and dysmnesia. Severe shock in the aged—such as that following hemorrhage, cardiac infarction, and surgery —can also lead to permanent brain damage and extreme dementia (3).

Carbon monoxide can be considered as a cause of anoxia because of its effect in reducing blood oxygen through the formation of carboxyhemoglobin. The characteristic chronic brain damage lesion is the destruction of the globus pallidus. Outside of suicidal attempts, carbon monoxide poisoning commonly occurs from exposure in automobiles or household heating, cooking, and refrigeration appliances.

After it had been established that exposure of the premature infant to oxygen concentrations over 40 per cent resulted in retrolental fibroplasia, some investigators noted that the blindness was accompanied by a higher incidence of mental retardation. Others found no such relationship and suggested that it was the association of retrolental fibroplasia and prematurity on one hand and prematurity and brain damage on the other which gave rise to the apparent association. In addition, there was the added environmental factor that blindness *per se* might be thought to reduce I.Q. because of its limiting effect on the learning experience. Parmalee, *et al.* (36) in a study limited

to blind school children between the ages of 5 and 9, were unable to demonstrate any difference in I.Q. between those blind as a result of retrolental fibroplasia and those blind from other causes. However they found a greater amount of mental retardation and neurological disorder in both groups than among sighted children. Another study by Norris (35) states that the children blinded by other causes have more mental retardation because of the high association of these conditions with neurological defects while retrolental fibroplasia produces the eye lesion as its only significant pathology. One must conclude that the weight of available evidence fails to incriminate excess oxygen as a cause of mental illness although the possibility has not been ruled out.

Trauma

Although persons with traumatic psychosis constitute only 1½ to 7 cases per 1,000 institutionalized patients (30, 6), there has been an increasing number of first admissions with this psychosis (27). Cases of traumatic psychosis in adults appear to be related to alcoholism, arteriosclerosis, and temperamental abnormality, but it is not known whether these conditions are caused by the trauma or constitute an underlying psychopathology which is exacerbated by it. Children have a 25 per cent better chance of surviving an equal amount of skull injury but no adequate follow-up has been made of the comparative mental effects.

A special study of penetrating brain injury showed that lesions of the frontal and occipital lobes did not produce a significant decrease in intelligence (46). However, lesions of the parietal and temporal lobes of the left hemisphere did result in marked deterioration in I.Q.

The more familiar pattern of brain injury following concussion can lead to a systematic disintegration of the mentality. The exact pathogenesis of the damage in non-fatal head injuries is not known, the most likely theories are the production of sudden cerebral anemia and the imparting of shear strains

to the brain (32a). Irreversible deterioration of personality and intellect and dementia are rare but dysmnesia, impaired concentration, and lessened spontaneity of thought are common. The particular form of brain damage from repeated concussion known as punch-drunkenness in boxers is characterized by many small brain lesions leading to a deterioration of memory and intelligence.

Poisons

Lead affects the nervous system as part of the cumulative end result of exposure over a long period of time with absorption occurring from either the alimentary or respiratory tract. Peripheral neuritis is a far more common symptom of lead poisoning than encephalopathy, but when it occurs it is associated with delirium and coma (32b). Children appear to be unusually susceptible and the resultant convulsions can leave permanent sequelae. Most of the other metallic and organic poisons produce an acute effect with neurological symptoms rather than a permanent psychoses or mental deterioration.

Alcoholism

Present estimates indicate that there are about five million alcoholics in the United States with a ratio of about 7 men to one woman (32c). Possibly one million of these have reached the stage where psychologic consequences have occurred. Malzberg (28) found that during Prohibition the percentage of alcoholic psychoses among admissions to New York State mental hospitals first decreased sharply and then increased after repeal to a figure of 10 per cent. Other more rural areas of the country show much lower percentages. Alcoholic psychoses are relatively higher in Negroes, rarer in Hebrews, and occur principally in middle age (14).

The more serious mental diseases appear to be more closely related to the consumption of spirits rather than to beer and wines. It is difficult to separate the effects of the brain damage from that of the intoxication. Heavy drinking for many years

results usually in a deteriorated personality, loss of memory, and even hallucinations. Some believe that most of the brain damage is not caused primarily by the alcohol itself but largely by the dietary deficiencies common in alcoholics.

The epidemiology of alcoholism itself is beyond the scope of this report. Suffice it to say that the search for personality types and environmental situations which predispose to alcoholism is being pursued actively. Although much has been learned, there is still great confusion and conflicting data. It is known that alcoholism can be preceded by a psychosis, a factor which makes it even more difficult to understand the significance of its association with mental disease.

Drugs

Barbiturates, cannabis, cocaine, and morphine are well known for their association with mental illness but there is no good evidence that their use is related to the development of any significant form of brain damage (32d). The habit is more prevalent among those who have psychopathic tendencies and the psychopathology of the acute and subacute states can lead to a progressive deterioration with poor prognosis but without clear cut evidence of brain lesion caused by the drug.

Infections

Bacterial meningitis can be caused by the meningococcus, pneumococcus, streptococcus, H. influenzae, M. tuberculosis, staphylococcus, and other organisms (51). H. influenzae is the most frequent agent associated with the disease in children except during periods of epidemics of other types. Meningitis in the pre-chemotherapy era was frequently followed by hydrocephalus, deafness, deafmutism, various forms of paralysis, epilepsy, and mental deficiency. In one series of 189 recorded meningitis cases, 12 per cent showed persistent cerebral damage and the majority of these had major mental retardation (2). Prevention of these conditions depends primarily upon prompt recognition of the bacterial meningitis with immediate treat-

ment with antibiotics before the lesions are extensive enough to result in permanent scarring.

Encephalitis is a term loosely used to describe a number of disorders which are associated with an inflammation of the brain. The exact etiology may be a virus which has a predilection for the CNS, or it may be an allergic or degenerative condition.

The epidemic encephalitides due to arthropod borne viruses which invade brain cells can result in severe brain damage and mental impairment. Equine encephalomyelitis is particularly damaging to infants with 54 per cent of its major sequelae occurring in those in the first year of life. St. Louis encephalitis has an incidence of major sequelae between 1 per cent and 8 per cent. Although these diseases are relatively rare, their occurrence is always alarming because of the great risk of the serious residual brain damage suffered by their victims (32e).

Mumps meningoencephalitis is the commonest example of a nonarthropod borne virus which invades brain tissue. It can occur in the absence of parotitis (15), but usually accompanies the classical syndrome. Army studies suggest that when a routine spinal tap is done, over half of the cases are found to have signs of virus invasion of the CNS, as compared with one-third who have clinical disease of the nervous system. Other studies dealing with other age groups indicate a far lower risk of meningoencephalitis in mumps. The basic lesion on necropsy studies is a perivascular demyelinization more closely associated with the post-infection encephalitis than with direct virus infection of the brain.

Mumps meningoencephalitis has a curious sex predilection with about seven times as many cases occurring among males as in females (24). Sequelae are rare, usually two or three per cent and then usually of minor nature although serious after effects have been noted. The great frequency of mumps, the fact that mumps occurs most usually in children who appear more susceptible to brain damage, the possibility that this encephalitis can occur during an episode of inapparent mumps

infection, the frequency of the CNS response during mumps, all give the disease added significance in a consideration of the relationship of brain damage and mental disease.

Other viruses which invade CNS tissue include the ECHO viruses, Coxsackie viruses, and others associated with the term "aseptic meningitis" (31). The epidemiology of many of these viruses is quite complex with a variety of animal hosts capable of playing a role in the ecology of the virus. Moreover, one cannot be certain that a given virus strain has a true cytopathogenic effect or that the isolation of a given virus from a case of encephalitis means that a true culprit has been found. It appears probable that many of these viruses can cause encephalitis and that residual brain damage does result from such infections. Further exploration of this field requires expanded use of tissue culture and probably the development of even newer techniques.

Measles is accompanied in about one case per 1,000 with a post-infectious encephalitis (31). The lesion is believed to be a "defense" mechanism of the CNS rather than a tissue invasion by the virus. Experimental studies have indicated a similar pathologic demyelinization response as an allergic reaction to tissue extracts. It has been presumed that the inflammatory reaction is the result of a tissue immunity and the plasma cell has been suggested as the site of action between the antigen and the neurone. If it is true that post-infection encephalitis is an allergic manifestation then the still unsuccessful search for a means of detecting the allergic predisposition and its therapy are of the greatest importance. Sodium salicylate and P. aminobenzoic acid are said to have some therapeutic effect. At the present time the best method of preventing this complication of measles appears to be the administration of gamma globulin.

Post-infectious encephalitis also follows smallpox vaccination (vaccinia), and immunization with some killed agents such as rabies vaccine and pertussis (31). The rabies vaccine effect is apparently associated with an allergic reaction to the contaminating extract of animal brain. Use of the new duck em-

bryo vaccine instead of the Semple material is now expected to remove this risk. The triad of fever, convulsions, and irreversible central nervous system changes following pertussis vaccine administration resembles that seen in some severe cases of pertussis. Although the symptoms have also been noted following the inoculation with diphtheria toxoid, typhoid, and influenza vaccine, pertussis vaccine appears to offer the greatest risk especially when given in the rapidly absorbed saline solution (16, 40, 4). Most of the children affected gave a history of central nervous system instability, and males appear to be affected twice as often as females. Children with a history of convulsions should be immunized only with monthly fractional doses and premature, frail, or ill infants should have the immunization postponed. It is not known whether the effect is due to a sensitization, a toxin of the organism, or primarily due to a constitutional susceptibility of the host. Although only a little over 100 cases have been reported in the literature, the persisting physical and mental morbidity rate of 30 per cent and the case fatality ratio of 15 per cent indicate that when it occurs this is a grave complication of a routine procedure.

Syphilis

Hahn, *et al.* (18), state that as the incidence of syphilis itself decreases, dementia paralytica is becoming something of a neuropsychiatric rarity. Approximately 5 per cent to 10 per cent of inadequately treated syphilitics will progress to late neurosyphilis. Between 1920 and 1950 the number of paretics admitted to New York State mental institutions dropped from 13 per cent of admissions to 2 per cent. The disease was uniformly fatal prior to von Jauregg's discovery of malaria therapy in 1917 but now is curable in some and partially remedial in many due to the advent of penicillin. Deaths from paresis in Great Britain between 1916 and 1955 dropped from 2,100 to about 200. In his series of 1,086 paretics, Hahn noted 60 per cent were simple dementing, 18 per cent manic, 6 per cent paranoid, 3 per cent with somatic signs only, and 7 per cent un-

classified. Even with specific penicillin therapy the death rate for paretics was still four times that of a comparably aged non-syphilitic group, a selective mortality which tends still further to decrease the prevalence of paretics. The best treatment is prompt detection with early and adequate treatment of syphilis in its early, pre-nervous system stage, and present syphilis control programs are undoubtedly responsible for most of the rapid fall of paresis. Congenital syphilis is also now exceedingly rare, and there has been no increase to parallel the recent rise in early syphilis. In one British series of 1,900 institutionalized mental defective children only 12 had a history of syphilis (5). The authors conclude that mental deficiency due to congenital syphilis will disappear.

Degenerative Encephalitis

The commonest form of degenerative encephalitis is multiple sclerosis, but the group also includes acute diffuse encephalomyelitis, Schilder's disease and Balo's concentric sclerosis (31). These are demyelinization processes which can be differentiated by micropathological examination from the post-infectious encephalitides. The etiology of these conditions is unknown, with allergy and certain predisposing factors believed to be of possible significance.

A number of epidemiologic studies have pointed out interesting associations which suggest etiologic hypotheses. A series of 39 families were studied in which there were three or more cases of multiple sclerosis. Others have found geographical differences with a higher incidence in northern areas, such as a six-fold higher rate in Winnipeg compared with New Orleans. Sutherland (43) suggests an ethnic predisposition in the Nordic in contrast with greater resistance in the Celtic race. It must be recognized that none of these epidemiologic studies is conclusive because of difficulties in differentiated diagnosis, small numbers, and lack of pathologic control. Despite the fact that experimental injection of myelolytic substances, ergotamine, potassium syanate, and other toxic agents may each produce

lesions suggestive of multiple sclerosis, no such mechanism has been shown to play a role in the human disease. Swank (44) suggests that multiple sclerosis is due to a high fat intake and substantiates his statement by an association of disease incidence with areas of high fat intake in Norway. However, other possible factors have not been ruled out nor has the theory yet received definite corroboration from studies of the response to adjustment of the diet of multiple sclerosis patients.

The incidence of intracranial tumors in childhood rises to a maximum at 5 to 8 years of age, falls, and then rises to a secondary peak at ages 10 to 12. Brain tumor incidence reaches another peak during the middle years of life. They usually develop slowly, giving the classical signs of intracranial pressure which may be delayed in the infant. Convulsions, difficult gait, and behavioral changes, such as lack of interest in school work, can be noted. Seventy per cent of patients with cerebral tumor are said to show some psychological disturbances, many of them in the early stages of the lesion. Recent surveys indicate an incidence of cerebral tumor of 4.6 per cent among inmates of mental institutions (23).

The glioma is the most common pathologic form, responsible for about one-half of all cases, with the spongioblastoma multiforme variety of glioma causing about one-quarter of the total cases. Meningiomas also appear in one-quarter of the patients afflicted with brain tumors. The remainder is made up of tuberculomas, gummas, metastatic, pituitary, acoustic, hypophyseal duct, and blood vessel tumors. The metastatic tumors appear as the most frequent tumor of this last group.

Deficiency Diseases

Cretinism has been observed in some mountain areas of Europe to occur with endemic goitre. It has later been found in inland areas over a wide area of the world. In 1933, Penrose estimated the frequency of hypothyroidism among mental defectives in institutions at 3 to 5 per cent (32f). Sporadic cretinism due to the absence of a thyroid gland still occurs with the

same frequency, but cretinism of the endemic type related to deficient iodine intake has decreased with iodization of salt and improved food distribution.

Congenital hypothyroidism can be diagnosed by the age of 3 months and always before 6 months if the characteristic symptoms of lethargy, constipation, respiratory distress, frequent infection, dry skin, thick tongue, hoarseness, and umbilical hernia are noted (26). In some instances even early treatment will not give a good mental result and in such cases an independent primary mental defect has been suspected (49).

Pernicious anemia is associated with a subacute degeneration of the brain. The pathologic process is unique and is distinguishable from that due to pellagra and other diseases involving cerebral white matter. The resultant mental symptoms are not characteristic, taking the form of a severe mental disturbance with paranoia or delirium. The pathogenesis appears related to a decreased cerebral metabolism due to a vitamin B12 deficiency and not to the anemia (47). The condition can be reversed if treatment with the vitamin is begun early. If one withholds treatment after the cerebral symptoms occur, while attempting to make a hematologic diagnosis, brain damage can result. Most improvement will occur during the first 3 to 6 months of therapy, and relapses associated with infections can be corrected by increasing the dosage of vitamin B12.

Diarrhea, anoxemia, or excessive salt ingestions may lead to hypernatremic dehydration (11). This condition can also arise from a central nervous system injury which alters the regulatory mechanisms for homeostasis of water and electrolytes. Hypernatremia in turn may result in subdural hematoma and brain injury. The hypernatremic condition is reversible if treatment to restore the proper electrolytic balance is begun before permanent brain damage occurs.

The earliest descriptions of pellagra made mention of the presence of mental symptoms, and pathologic studies have confirmed the presence of marked changes in the Betz cells of the motor cortex, the frontal lobes and the periventricular

areas (32g). Pellagra arises from a multiple deficiency of vitamins of the B group, including thiamin and riboflavin, but especially of nicotinic acid. Chronic alcoholics, because of their poor diets, appear to be especially susceptible to pellagra which appears characteristically in any low economic population on a cereal diet. The disease becomes worse in the spring, probably because it follows a winter diet deficient in fresh vegetables.

Treatment by nicotinic acid usually results in improvement of the psychiatric symptoms if the brain damage has not progressed too far. Therapy with additional components of the B vitamin group must be approached cautiously because it may upset the vitamin balance and lead to an exacerbation. Pellagra psychosis is decreasing dramatically in incidence in this country with the general improvement in diet.

Wernicke's encephalopathy (32h) appears to be likewise associated with vitamin B deficiency, perhaps primarily a thiamin deficiency. Hence it can be looked upon as a severe form of beri-beri. Congestion and hemorrhages in the gray matter of the brain-stem and mammillary bodies of the hypothalamic region appear as the chief pathologic findings. The disease occurs with severe alcoholism or malnutrition and appears to be an acute response to a low level of thiamin in the body, superimposed upon a background of nutritional deficiency. Since the disease is a late manifestation of a long standing nutritional disorder, therapy with thiamin usually does little to reverse the mental disturbances.

A recent British study suggests an association between intelligence and nutritional adequacy among school children (21). Seventy-three per cent of children in schools for the educationally subnormal were below average in weight and 68 per cent were below average in height. This is a poorly controlled study, and it is obvious that such a finding can only be useful in suggesting new paths for epidemiologic exploration. It is mentioned here to fill a gap in the discussion of nutritional deficiency. Although severe deficiency can result in mental disease, such situations are becoming increasingly rare. Modern effort

must seek to explore the effect of lesser degrees of sub-optimal diet. Mental hospitals report that patients admitted in a poor nutritional state improve with dietary supplements (17).

Convulsive Disorders

Epilepsy, the most common of neurological disorders, affects 1,500,000 Americans. The low threshold of the neurones subject the brain to frequent mass discharges, which take such forms as attacks of grand mal or petit mal. In the psychomotor form of the disease the temporal and frontal lobes are affected, leading to "automatisms." As is true in all forms of epilepsy, the patient has amnesia for his psychomotor attack.

Seizures may be related to a number of factors which damage neurones, such as head injuries, congenital defects, birth injuries, brain infections, brain tumors, fever, and defects in cerebral circulation. Such lesions can produce a small area of scarring in the brain which serves as the source or focus for the start of an epileptic attack. In most cases the etiology is unknown, and hence 70 per cent of cases are termed idiopathic.

Hereditary factors are traditionally believed to play a role since if one of a pair of identical twins without known prior brain damage was epileptic the other was also epileptic in a majority of instances (19). Even among those whose epilepsy follows a brain injury, a family history of epilepsy is three times as common as among the general population. For idiopathic epilepsy the incidence is said to be seven times as great in the near relatives of the patient. However, other factors could account for this apparent genetic relationship, such, for example, as the greater frequency of prematurity among twins, which, itself, is related to greater risk of brain damage.

Studies of the prenatal and perinatal period indicate the existence of more abnormalities for epileptic children than for matched controls (25, 37). It is possible that amino acid metabolism plays a role in epilepsy but the experimental findings have not yet demonstrated the mechanism of action. The search for some chemical explanation of neurone hypersensi-

tivity is being pursued actively and is the most attractive hypothesis which could explain both the seizures and their response to the anti-convulsant drugs.

An epileptic attack following a high fever from a non-specific infection is most common in the child under age 3. Therapy to reduce the fever is indicated, since a certain proportion of cases develop the idiopathic form of epilepsy at a later date, especially if the first febrile convulsion occurred in infancy. In addition, a tendency toward repeated febrile convulsions is the rule and may lead to brain damage. Hence continuous anti-convulsant drug therapy up to age 3 or 5 is recommended by many after even one such attack; by all after two or three. The younger the child at the onset of convulsions, the more likely he is to become mentally retarded (23). In later life mental deterioration is more apt to occur among those epileptics whose disease is associated with injury to the nervous system than those with idiopathic epilepsy. Mental impairment is most commonly seen in the psychomotor syndrome, next in grand mal and is least likely with petit mal.

Convulsions from any cause, if severe, repeated or prolonged, can lead to anoxia of the brain with damage to the neurones. The goal of therapy must, therefore, be aimed at reducing the number and duration of the seizures. Caution should be used in withdrawing drugs completely even after years of freedom from symptoms, since there is a 50 per cent chance of recurrence. Even with adequate drug therapy, 75 to 80 per cent control of seizures is the best that can be expected. Despite the association of mental deterioration and epilepsy, 67 per cent of epileptics are found to be of average or superior intelligence, 23 per cent slightly below normal and only 10 per cent grossly deficient (50).

Cerebrovascular Disease

During the past decades there has been a striking increase in the incidence of psychosis associated with cerebral arteriosclerosis. In New York State mental institutions, the propor-

tion due to this condition rose from 7.8 per cent in 1920 to 14.3 per cent in 1930 and 19.9 per cent in 1940 (29). These relationships are not appreciably changed after they have been standardized for age: 21.3 per 100,000 population in 1920, 44.4 in 1930, and 66.7 in 1940. The arterial disease decreases the blood supply to the brain with resultant neurone necrosis and increases the risk of infarcts and brain hemorrhage which cause even more extensive brain damage.

The epidemiology of cerebrovascular disease has been studied but the findings are not very revealing. One of the most extensive investigations has been reported by Takahashi and coworkers (45) in Japan. This particular country has a low mortality from coronary heart disease—the chief cause of mortality of Occidental countries—and cerebrovascular disease is now its leading cause of death. Takahashi found the incidence highest in the northeastern areas of the country except for Hokkaido. The distribution of average blood pressure, hypertension and hypotension seem to parallel the death rate from cerebral hemorrhages, if one accepts the general belief that hypertension is a predisposing disease. The authors conclude that low outdoor and indoor temperatures are responsible for the vascular phenomena. They also note that areas of high incidence are those whose inhabitants eat more rice and salt and less vegetables. These studies are also poorly controlled and the findings are of importance merely because they suggest further explorations.

Ecker (10) studied 20 patients with cerebrovascular disorders and found that 13 had a history of longstanding personality disorders preceding a stroke, in 15 special emotional stress immediately preceded the stroke, and in 8 cases both factors were present.

Vasospasm of the larger cerebral arteries can lead to cerebral edema and permanent neurologic disease (38). It is now believed that most first serious episodes of stroke are preceded by one or more "little strokes" which may be vasospasms, small thrombi, emboli, or cerebral insufficiency associated with nar-

rowing of the arteries of the brain (42, 8). The administration of anti-coagulants may decrease the incidence of thrombosis. However, their use also brings the danger of hemorrhage and may lead directly to further brain pathology. Nevertheless, anti-coagulant therapy appears to exert a favorable influence on the future of patients who have suffered their first stroke (48).

An interesting review of hospital first admission rates for senile psychosis has been performed in Onondaga County, New York (33). Significant differences were found in the sex specific rates between urban Syracuse (with the highest rates) and the more rural remainder of the County. Even in the latter the villages had higher rates than their truly rural surroundings. The village with the lowest admission rate was the one with the highest concentration of foreign-born—white persons of Italian, German, and Polish extraction—a finding which was also noted in the analysis of the data for urban Syracuse. The authors note that these findings could be caused as well by an in-migration of the mentally ill into the high prevalence areas or a higher tendency toward hospitalization from these areas, as by a true etiologic relationship based upon environmental or ethnic differences between these areas. Their own studies do indicate that admission rates tend to be higher for populations which live within twenty miles of a mental hospital. This effect appears to be diminishing, and it may be a chance association with other variables which are significantly related to the prevalence of senile psychosis.

The current state of knowledge of the mechanisms possibly related to the occurrence of cerebrovascular disease have been reviewed by Scheinberg (41). An extensive account of these is beyond the scope of this report, and present knowledge is too inadequate to give definitive answers. Similarly, a discussion of the epidemiology of the two major forerunners of cerebrovascular disease, hypertension and arteriosclerosis, is too complex to be included here. It is worth noting that arteriosclerosis of the coronary arteries has a different geographic and ethnic

distribution from that of the arteries of the brain. The confusion which exists in reaching an exact clinical diagnosis of both of these conditions further complicates the problem for those performing epidemiologic studies in this realm.

Conclusion

This review of the relationship of brain damage after birth and mental disease will be concluded with the same general impressions with which it was begun. Although many clinical and pathologic conditions associated with mental disease have been identified, the epidemiology of these underlying conditions requires much more exploration. Present data are sufficient to be useful in controlling much brain damage due to jaundice, anoxia, ischemia, poisons, alcoholism, bacterial and treponemal infections, some varieties of deficiency diseases and epilepsy. They are inadequate to offer much against the virus diseases, trauma, degenerative conditions, most tumors, and cerebrovascular disease. It must be admitted that the greatest number of patients suffer from mental disease associated with brain damage which is still not preventable. The hope for an understanding of these mechanisms sufficient to permit ultimate control lies in future research. Epidemiologic studies should comprise a major portion of this research effort.

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Dr. James: I have one comment to make, namely, that this particular field, as I am sure everyone knows, has an extremely voluminous literature, and the very size of it made me more terse than perhaps I should have been.

Let me just set myself up for real criticism by saying that the selection of the papers to be noted was done by me on purpose, so that if the selection is a poor one, I am to blame.

There are a large number of references that could have been mentioned that were purposely omitted merely to keep it in some manageable proportions, and in re-reading it several weeks after the event, I was a little surprised at its terseness and with the fact that I had selected very few references in many controversial areas.

Discussion

Dr. Benjamin Pasamanick: I find myself in the same position that the other discussants did, that is, not knowing the field under discussion very well. Therefore my comments will have to center on Dr. James' paper rather than adding much to what he has written.

In the first place, I found this particular area in a rather interesting state. There is much greater variation in the state of knowledge and investigation in this area in contrast to the social, psychological, and cultural areas, both as to the variables involved and as to the hypotheses to be considered.

For instance, let me point out that in such conditions as measles encephalitis, measles is a necessary condition by definition but I think we can state that when we find retardation immediately following upon measles encephalitis there is very little doubt about the causative relationship.

However, when we come to the predisposing and precipitating factors for encephalitis and brain damage we have very little knowledge in this field, and really poorly defined hypotheses for epidemiologic investigation.

This is true of many of the factors discussed in this particular review. After reading Dr. James' paper and reading some of the references he cited, I was surprised by this finding and somewhat consoled for our own deficiencies to discover that so many of the studies were poorly defined, lacked controls, and definitiveness. Much needs doing and redoing epidemiologically.

I have a few comments which refer to specific points in the paper. I agree with Dr. James that the role of hyperbilirubinemia is still not well understood. I think that we ought to recommend more routine maternal and paternal incompatibility studies because, by determining the presence of incompatibility and antibodies in the mother, we have the capacity to predict when jaundice is likely to occur and prepare for exchange transfusions.

An interesting finding that I have gleaned from some of the pediatricians is that ABO incompatibility seems to be decreasing or almost disappearing with the cessation of the administration of Vitamin K and this then brings up the whole matter of iatrogenic conditions.

Gantricin administration, for instance, in newborns also seems to be implicated in this whole sensitivity area.

I think as we get more and more specific therapeutic agents and do more and more to patients, we have to think more often of the possibility of doing damage. There seems to be competition in the enzyme systems of the premature and the newborn in response to the administration of some of these substances. I think that there seems very little question at this time that Vitamin K is damaging.

Day, in a further remark on the administration of glucuronic acid, indicates that glucuronic acid administration simply doesn't work.[1]

[1] P. 85.

Following this, is a discussion of anoxia, anoxemia and ischemia.[2] Dr. James makes reference to Darke's work. In that regard I would like to point out that Darke eliminated cases with positive neurological findings. Those are just the kinds of cases which would have had intellectual retardation. While Darke still found significant changes, Keith and Norval later did exactly the same thing in eliminating cases with positive neurological findings in a similar study of the sequelae of natal apnea, but they did not find any differences. They also reported, in a somewhat better controlled study, that they didn't find any effects of anoxemia at birth with later behavioral functioning in infants.

We, too, do not seem to find this when we eliminated the prior occurring complications of pregnancy and prematurity.

In Dr. James' discussion of blindness and retrolental fibroplasia and effects of blindness on development,[3] I think the evidence indicates that blindness in and of itself probably does not have much if any effect on intellectual potential. I think the reason so much defect is found in non-premature blind children is that most of these are due to congenital neurological defects, and when we have congenital defect, we usually have more than one in the central nervous system, and this probably accounts for the intellectual deficit. Clinically we seem to have a difference between defects distal to the retina, and those involving the retina, because the latter being a direct outgrowth of the central nervous system would probably accompany other congenital central nervous system defects. In our premature study, I don't think we found any difference in the amount of defect between those with, and those without, retrolental fibroplasia in infants under 1,500 grams, so that I don't think that oxygen administration to the newborn has much effect on the central nervous system.

When we come to physical trauma,[4] Dr. James remarks that there is an increasing number of first admissions of traumatic psychosis. How much of this is due to better diagnosis and also to saving more individuals from death? With regard to lead intake in children, we have surprisingly little proof that lead causes mental defect. The evidence, although seemingly good, is not really definitive.

I think we ought to spend a bit more time on such conditions as

[2] P. 86.
[3] P. 87.
[4] P. 88.

alcoholism and cerebrovascular diseases because these really contribute enormous numbers to the mental hospital population and to disability in general, in contrast to some of the other conditions mentioned in this particular paper.

Let me give you some indication of the complexity that exists in some of the variables under discussion. When we come to the remarks on infections as causing brain damage, matters are not quite as simple as they appear. For instance, we have found that in brain injured children we get a significantly higher rate of illness, both hospitalized and non-hospitalized, during the first year and probably afterwards. A good many of these illnesses are infectious in nature, so that this variable of brain injury must be factored out even in a discussion of infection as a post-natal factor. Is an already injured brain more susceptible to infection?

In addition to this, since we have relationships between socio-economic factors and infection and brain injury; and, in turn, intellectual functioning with socio-economic factors (all of which confound the effects), matters are not as simple as they might be, in epidemiologic studies, even in something as seemingly clear-cut as the relationship of infection to brain damage.

As to syphilis, I wonder what is going to happen as our vigilance decreases in case finding in syphilis? I have found that the pediatricians are beginning to forget about syphilis in differential diagnosis of conditions in children, and they have to be caught-up on this now and then because we still find congenital syphilis and even primary syphilis in children.

In the deficiency diseases, when we come to cretinism, we are beginning to suspect that the results of treatment with thyroid in cretinism are not related to time of administration of the medication. I think that we have found higher intelligence quotients in many early treated cases because these occur in children coming from higher socio-economic backgrounds, those that get medical care earlier. We continue to find a large number of defective children, even with quite early institution of thyroid treatment. On the other hand, there are a large number of children who seem to do quite well even when thyroid is administered later during infancy.

My remarks however ought to be confined wholly to infancy. If we start giving thyroid to three or five-year old children, I think we probably would be too late.

Dr. James remarks on an association between intelligence and nutritional adequacy among school children.[5] Again this is not as simple as it appears. A quite possible explanation is that the children who are physically subnormal because of socio-economic status, are also mentally subnormal because of the same reason, and nutritional deficiency is merely associated with both. However, the situation is probably confounded in that all three variables are involved.

Dr. James speaks of hereditary factors as undoubtedly playing a role in epilepsy because of the findings in twin studies.[6] I am not so certain about the hereditary factors on the basis of this evidence. For instance, we have known for a long time that identical twins are more subject to brain damage than non-identical twins so that a higher rate of concordance would be expected for monozygous and dizygous twin pairs. The evidence also seems to indicate that twins have a much higher rate of epilepsy than do singletons in the population. I would like to point out that family histories of a disease are notoriously biased in the direction of the disease under scrutiny since histories of the disease in cases and controls are not secured under comparable circumstances, and that the family history evidence of epilepsy is therefore not a very good one.

I have just one final comment on cerebral vascular diseases. As to the striking increase in the incidence of psychosis associated with cerebral arteriosclerosis, I think we all recognize that this may largely be due to failure to die from some other cause, such as infection, and also to lack of chronic disease facilities. The inadequacy of facilities for care of the aging causes admission to mental hospitals as one of the few places you can put chronically ill individuals.

This brings up the whole matter of reversible damage, which has largely been omitted from Dr. James' review. I wonder how many patients labeled as psychosis with cerebral arteriosclerosis, or senile psychosis, are admitted to mental hospitals because they had one or more chronic disorders such as heart disease? Being bedridden for lack of adequate care, they became confused as a consequence of some minor anoxemia, and were quickly shoved into mental hospitals because they could be taken off local budgets and put onto state budgets, where they remained confused and psychotic because of inadequate care.

[5] P. 97.
[6] P. 98.

I think this is merely an indication of the need for more discussion of the two conditions that I mentioned—alcoholism and cerebral vascular disease.

SUMMARY OF THE GENERAL DISCUSSION

1. In his paper, Dr. James considered that hereditary factors undoubtedly played a role in epilepsy. There was disagreement on this point. Epilepsy is no longer thought of as a disease and, therefore, there is no reason to expect results from genetic investigations. Many of the ideas about epilepsy, which are still circulating, are based on old studies of twins in Germany by Kornwall. He worked with institutionalized epileptics who in most cases were also mentally deficient so that the data were heavily biased, being really studies of mental deficiency with seizures as accompanying symptoms. In Sweden, a committee of various specialists is presently engaged in revising a 17th century law that prohibited so-called idiopathic epileptics from marrying, since evidence, in part based on studies by Bjornstrom, indicated that there is no reason to maintain the law.

It was doubted whether such a thing as idiopathic epilepsy existed in the sense that seizures arose "spontaneously"; this suggested a genetic etiology in the absence of other apparent causes. From the studies done in Sweden it appeared that such seizures could be traced in the histories of the patients to a variety of causes, such as alcohol or infection.

Finally, it was noted that there is no good evidence, either, for a genetic factor that predisposed to seizures in conjunction with any specific cause. For example, in cases of battle injuries to the head only a small percentage of cases developed traumatic epilepsy. But if such cases of a specific known etiology were compared with cases of unknown etiology it was found that there was the same incidence among the siblings of both groups, about 2.5 or 3 per cent.

In the case of cretinism, on the other hand, some recent studies seem to indicate a genetic factor, especially where there was inbreeding as, for example, in the valleys of Switzerland and Austria. The disease then is not entirely a matter of thyroid deficiency and iodine insufficiency, but is apparently complicated in some cases by a recessive genetic factor.

2. Meningococcus meningitis needs to be mentioned with syphilis as a disease that could very readily be overlooked because it has generally been so well controlled. Recent experience in Maryland showed an increase in deaths from the disease, and it is therefore highly likely, though not demonstrated, that there is a parallel increase in the number of persons suffering brain damage from the disease, such as mental deficiency or deafness. The disease must still be considered dangerous and a high index of suspicion for it should be maintained in diagnostic work-ups.

3. The relationship of blindness to mental retardation was discussed. Since in our society, a blind individual tends to be marginal in a number of ways, might not this social factor affect the individual from infancy, contributing to whatever mental retardation that occurs?

4. It was suggested that brain damage possibly has a bearing on symptoms labeled as psychoneurotic. While this is a difficult area, it is an important one. Apart from the longitudinal studies presently being done abroad which offer some bare suggestive evidence of such a relationship, there exists no evidence to this effect, a fact that has been interpreted in support of the purely psychological explanation of psychoneurosis. But is this lack of evidence due to none having been found or because not enough effort has been expended?

5. Some pointers for research in this field of damage to the brain were made. While it is believed that early detection leading to prompt treatment is the key controlling many conditions, it was noted that in some the evidence for this belief might be spurious. This was suggested by McKinney in Canada, when he proposed that the decisive factor in breast cancer is the speed of progress of the disease. While it might seem that the time of making the diagnosis affects the prognosis, actually it is the progressiveness of the disease that affects both of these other variables. Thus the more rapidly growing-type of cancer tended both to be seen late and to have a poor prognosis. The same situation might occur in cretinism. If so, the time of administration of thyroid was a relevant question.

6. Another point relevant to a better understanding of cretinism was illustrated in the relationship between sickle cell anemia and malaria, where the same factor that is responsible for vulnerability to the anemia also gives protection against malaria. Thus it might be worth inquiring as to whether there is some biologic "good" asso-

ciated with cretinism which acted as a defense mechanism against another harmful contingency.

7. The enormous French literature on alcohol and psychosis, which uses a somewhat different approach from that of the Anglo-Saxon world, remains completely ignored in both the United States and Britain. Much the same could be said of the very extensive Japanese genetic literature on twin studies. While there were some barriers in communication or comprehension, there seemed to be no effort made to overcome them. This is a defect in outlook and mode of work, since attention which is confined merely to what is congenial is evidence of cultural bias on the part of investigators.

Some impressions of the French studies, based on fragmentary acquaintance of the literature, was offered. A number of studies compared admission rates for alcoholic disorders by geographic areas and by subsections of the population, finding striking differences between, for example, various groups of immigrant laborers and native Parisian laborers; between wine-growing and other districts, or in relation to toxic factors affecting the wine harvest from one year to the next.

8. Other specific substances related to brain damage not discussed by Dr. James in his paper, included benzedrine, whose effects in addicts were seen in admixture with the psychopathic traits that made persons prone to addiction. Benzedrine psychosis was increasingly being taken into account in Britain, while Japan's considerable benzedrine problem stemmed from the forced use of the drug during the war as a means of increasing production. Benzedrine has also been implicated in acute psychotic episodes in non-addictive cases, where attacks were diagnosed as acute schizophrenia, and this experience shows the importance of looking for benzedrine as a possible organic factor.

Prominent amongst the other drugs in common use that should be considered with suspicion are the bromides and tranquilizers.

Some evidence was found in Britain that prolonged anesthesia in elderly patients accelerated mental deterioration. However, very little work has apparently been done on the matter.

9. Among deficiency diseases, protein deficiency raised challenging questions. The mental effects of kwashiorkor during the acute stage were striking; and there was the impression that severe cases produced lifelong sequelae. This suggested that in areas where

"kwashiorkor" as such had not been reported (perhaps in the South or the Southwest of the United States) similar protein deficiencies might be going by some other name.

10. Alcohol, apart from its direct role, needs to be considered because of its enormous influence in traumatic brain damage. Figures that indicated the extent of the problem were alarmingly high. It has been said that as many as 80 per cent of fatal automobile accidents involve drunkenness, while 25 per cent of all admissions to Bellevue Hospital directly involved alcohol. In associations of multiple factors in etiology, alcohol holds a most prominent place.

Dr. James: One of the points of reference for this paper was the occurrence of brain damage. Although the drugs which have been mentioned by several of the discussants can cause acute conditions (Point 8), I was unable to find clinical evidence of their relationship to the development of detectable organic brain damage.

The fact that this report did not include a more extensive discussion of the major conditions is a real criticism, and I was well aware of this while writing the paper. The conditions with the best known epidemiology appear to be those with the lowest incidence and prevalence: jaundice and encephalitides for example. Although the major problems, like alcoholism and cerebrovascular accidents, are the subjects of a voluminous epidemiologic literature, this literature is confusing and offers very few lines of clear evidence. Even the best of it seems only to suggest a few hypotheses whose value rests mainly upon the fact that they suggest where additional studies should be performed.

The Takahashi paper (45) intrigued me because it did present a definite hypothesis. However, the usual bias due to the inadequate diagnosis, pathologic controls and follow-up makes it impossible to accept this hypothesis as anything other than an interesting problem for further study. I included it because, as a generic paper in this field, it illustrates the difficulties one encounters in performing epidemiologic studies, the weaknesses of the final conclusions, and the huge task it will be to pursue these leads by an adequate epidemiologic investigation.

In general, every one of the underlying conditions discussed in this paper is itself a subject for extensive epidemiologic study, and these pathologic complexes are related to much more than brain damage

and mental disease. A discussion of cerebrovascular disease will lead into a review of the differences in the epidemiology of atherosclerosis when it occurs in the coronary arteries, the cerebral arteries, or aorta. It would have been an enormous task to have included a useful review of this subject and, as was pointed out, it was considered beyond the scope of the present discussion.

I think the comments on cretinism (Point 1) illustrate a problem in epidemiologic reasoning which has been noted in some of the earlier discussions today. When a cretin did not improve after the administration of thyroid, he was given a different diagnostic label. It was said that his cretinism was due to a condition that would not respond to thyroid. Although this is circular reasoning, it can be a significant first step in the classification of disease and help define different epidemiologic groupings for further exploration. At present it leads to confusion if one attempts to explain the proper role of thyroid function in patients now classified as cretins.

It was noted in the report on jaundice that the erythroblastotic child can get into difficulties because of several possible mechanisms. His red cells coated with antibody may not carry oxygen as well as normal red cells, leading to brain damage from anoxemia. On the other hand, the bilirubin itself can be directly toxic to the brain. It is difficult to be certain which factor is the cause of the brain damage. This illustrates another difficulty encountered in drawing conclusions from the existing reports in the literature.

Dr. Pasamanick in his opening remarks noted correctly that the British study on nutritional deficiency was designed poorly and does not permit one to draw etiologic conclusions. The investigation was included only to illustrate a general approach which, if properly performed, might be useful in a study of the epidemiology of these conditions.

Although many of the well-outlined conditions associated with mental disease occur rarely, it is possible that their more frequent sub-clinical stages might be related to mental diseases to a greater degree than we now suspect.

The exploration of the role of suboptimal amounts of nutrients or serum levels of bilirubin slightly above normal as possible agent factors in brain damage might be a fertile field. The studies of the New York group on the effect of slight elevations of concentrations of bilirubin in retarding development of the newborn are suggestive.

Our understanding of the epidemiology of brain damage due to the infectious agents, as some of the discussants have noted (Point 2) is far from complete. We do not know the basic mechanisms involved in pathogenesis; we do not know why one person develops brain lesions while another, with a more severe degree of infection, does not. Whether this is due to host factors, such as a genetic susceptibility or a temporary change in the physiologic state, is not known. It is true that most of these are rare conditions, but an elucidation of the basic mechanisms involved in the different host responses might do a good deal to improve our knowledge of the causes of brain damage.

As far as the diagnosis of syphilis is concerned, I am not aware of any clear evidence that a lowering of the index of suspicion has resulted in any greater incidence of brain damage (*see* Point 2). It is true that we are having more early syphilis, although still far less than we had two decades ago. However, we have yet to note any increase in late syphilis during these past few years, and its decline has continued to the point where symptomatic tertiary syphilis is fast becoming a clinical rarity.

I would like to close these remarks with a few comments about the field of organic brain damage and mental disease. Of all of the categories of mental illness, this might seem to be the one most easily grasped and most easily attacked. Our review has indicated that it suffers from the same problems of diagnosis, reliability, and validity which were noted in our discussions of each of the classifications of mental disease.

The need for cohort studies is obvious. The fact that very few good ones have been done is discouraging to today's reviewer but offers a challenge to tomorrow's investigator. It is doubtful that we can learn a great deal more by continuing to review in depth the many reports, largely based upon retrospective studies, which have supplied the mass of existing data in this field. Rather let us spend our efforts in fresh starts, possibly based upon some of the intriguing hypotheses which do evolve from a review of the past literature, and utilize statistical designs which will permit more assurance in our chains of inference.

DURATION-OF-RESIDENCE ANALYSIS OF INTERNAL MIGRATION IN THE UNITED STATES[1]

KARL E. TAEUBER[2]

KNOWLEDGE of migration can be advanced by the collection and analysis of new types of data, as well as by further analysis of the existing types of data. Much effort can be profitably devoted to the development of new approaches to available data. (1, 2) Nevertheless, many of the questions we may pose about internal migration cannot be answered by analysis of the census data or the Current Population Survey annual residential mobility series. New types of migration data are needed, based on additional migration questions. This paper discusses the migration information provided by a question on duration of residence, and presents the first national migration data derived from this approach.

Comparisons of current residence with residence at a fixed previous time, as in the migration questions in the 1940 and 1950 censuses and in the CPS, overlook multiple (including circular) migrations by individuals. From decennial censuses can be derived estimates only of net migration. Both approaches are thus directly concerned with population redistributions, and only inferentially with specific moves. Both approaches permit the delineation of some of those persons who have made at least one move, but do not differentiate the migration experiences of the great majority who have the same residence at one, five, or ten-year intervals. The duration-of-residence approach, on the other hand, provides direct information on a portion of the actual migration history of each individual. The duration of residence represents the length of time since the last move. Duration-of-residence data thus provide information on the latest segment of the residence history of each individual.

[1] Paper read at the annual meeting of the Population Association of America, Washington, D.C., May 7, 1960.

[2] Biometry Branch, National Cancer Institute, National Institutes of Health, Public Health Service, Department of Health, Education and Welfare, Bethesda, Maryland.

In the United States, duration-of-residence data for particular groups have been collected occasionally. Four examples may be cited. In the Massachusetts State Census of 1895, durations of residence in the town, the State, and the United States were ascertained. (3) The data were collected primarily because of the need for knowledge about immigrants. Durations of residence were listed separately for native born and foreign born, with more detail on durations in the State and in the country than in the town of current residence. Discussion of the data focused on the relationship between stability of residence, "the question of citizenship," and "various other problems of our social economy."

> When, therefore, an appeal is made to those who may possibly hold the elective franchise in Barnstable County, there are less than four in every 100 to whom such an appeal may be addressed who are of foreign birth of less than 10 years' residence in the United States; but in Middlesex County there are about 15 in every 100, nearly one in six, of this class, whose acquaintance, by direct contact, with our institutions, and with the civic policy of the United States does not antedate the beginning of the decade ending in 1895.

Goldstein also utilized duration data in the context of a concern with the problems of the maintenance of social and cultural stability in communities characterized by high migration rates. (4) He was studying internal migration rather than immigration. On the basis of the presence of names in successive city registers, Norristown, Pennsylvania, residents were divided into those with durations of residence in the City of less than 10 years, 10 to 20 years, and more than 20 years. These data contributed to one of his major conclusions: "Thus it was only the migrant group which was highly unstable; and a large segment of the population, through its continuous residence in Norristown, gave continuity and stability to the population of the community." Data only on current migration rates do not distinguish the existence of a residentially stable segment.

Rider and Badger used a duration-of-residence approach to

draw conclusions about a general feature of residential mobility. (5) The data were derived from a sample of dwelling units in the Baltimore Eastern Health District which was surveyed annually for three years. Of the original householders, 84 per cent, 75 per cent, and 69 per cent were still in the same dwellings at the end of one, two, and three years, respectively. These and other data support the conclusion that, "the probability of moving within a specified time . . . decreases as the length of maintaining the same residence increases." Thus residential mobility during a given time period is not independent of previous mobility experience. Persons who have not moved recently are less likely to move in the future than are those who have moved recently. This is a more general statement of Goldstein's proposition that a small proportion of frequent migrants accounts for a high proportion of all migration.

A recent paper describes procedures for collecting residence histories of decedents. (6) The paper included some discussion of the duration of residence at the usual place of residence listed on the death certificate, for the purpose of evaluating the utility of usual place of residence as an etiological factor in analyses of causes of death. Duration-of-residence data were used to distinguish those with short durations at the usual place from those with long durations. Approximately three-fourths of the sample of 400 decedents had durations of 20 years or more, but few of them had lived their entire lives in one place.

The study of 400 decedents in Pennsylvania served as a pretest for a National Lung Cancer Mortality Study. The Study is being undertaken to ascertain the interrelations between residence, tobacco smoking habits, and lung cancer mortality. Residence information was collected for a national sample of decedents from lung cancer. To permit computation of death rates, corresponding data were required for the living population. The data were collected in a Supplement to the Current Population Survey of May, 1958. This Residence History and Smoking Habits Schedule was sponsored by the National Cancer Institute, in cooperation with the National Office of Vital Statistics

and the Bureau of the Census. The schedule represents a unique attempt to gather a complete history of the places of residence and time at each place from a representative national sample. The duration at the current place of residence is only a part of the residence history. Later reports will take up other portions of these data. The present tabulations are only of duration at current place, without regard to previous place of residence or any other residence history items. Obviously the complete residence histories offer much scope for the development of longitudinal analysis of the migration experience of individuals. The duration-at-current-place data may be regarded as a link between the comparison-of-residences approach to current migration and population redistribution and the complete residence history approach to lifetime patterns of migration.

The meaning of duration-of-residence data, like other migration data, depends on the way migration is defined. The duration data in the three local studies cited derive from three different definitions of what constitutes the previous move. In the analysis of the Massachusetts data, familiarity of immigrants with the political process was assumed to depend not on residence in a particular town so much as on residence any place in the State. Thus the analysis focused on duration of residence since moving from elsewhere into Massachusetts. Goldstein was studying the patterns of mobility of residents of a particular city, and his duration data refer to length of continuous residence in Norristown. For the Eastern Health District, the data record duration of residence within individual dwelling units. Any residential mobility, whether a shift from one apartment to another or a cross-country move, thus interrupts the span of continuous residence.

The procedures described for the Residence History Supplement record duration of residence in an urban or rural place.[8]

[8] Questions for Determining Duration of Residence.
1. Location of present residence:
A. City or other urban place:
Place ——
County ——

(Continued on page 120)

Local moving within a place is ignored. This procedure focuses on length of residence within a political unit, the duration since moving into the city or other place. It corresponds most closely to Goldstein's approach in the Norristown study. This definition sharply differentiates the 1958 data from those collected in the 1960 Census on duration of residence in the house or apartment. The new Census data emphasize total residential mobility, and are designed primarily to provide information on housing turnover rather than population mobility.

The difference between the two approaches can be demonstrated by a comparison of the 1958 duration-in-place data with duration-in-dwelling data for April, 1952. Table 1 presents data for roughly comparable categories from the two Surveys. Durations in dwellings are considerably shorter than durations in places. The greatest differences between the two types of data occur for the duration category, entire life. Twenty-six per cent of those 18 and over report having lived their entire lives in one place, whereas only 2 per cent have remained in the same dwelling unit. The differentials between these two sets of data are somewhat larger than expected from the magnitude of the differences between total mobility and inter-county migration in the annual Current Population Survey data. If the several types of data could be compared for corresponding categories for the same time period, speculations about the reasons for the differentials might be fruitful. Here it is sufficient to note that the duration-in-place and duration-in-dwelling data portray quite different aspects of residential mobility.

The 1958 duration-in-place data may also be contrasted with data from the Current Population Survey on change of residence between April 1, 1957, and April 1, 1958. Persons with a

Is this residence inside the limits of (Place)?
If no, is it inside the limits of some other city, town, or village?
B. Not in city or other urban place:
County ———
Is this residence on a farm?
2. Have you lived in (Entry in Item 1) all your life?
If no, how many years have you lived continuously in (Entry in Item 1)? ——— Years.

Duration in Place / Duration in Dwelling		All Durations	(Months) 0–11 / 0–11	12–59 / 12–63	60–119 / 64–135	120+ / 136+	Life / Life
18+	Place	100	5.3	16.0	13.0	39.6	26.1
	Dwelling	100	19.7	35.7	19.9	22.8	1.8
18–24	Place	100	11.3	22.5	10.0	15.4	40.8
	Dwelling	100	36.2	34.5	13.2	11.3	4.8
25–34	Place	100	8.0	26.9	17.2	19.9	28.0
	Dwelling	100	28.8	49.5	14.3	6.1	1.2
35–44	Place	100	4.2	16.5	17.6	37.0	24.7
	Dwelling	100	17.6	39.5	25.3	16.4	1.1
45–64	Place	100	3.0	9.4	10.5	54.4	22.7
	Dwelling	100	11.5	27.6	23.8	35.8	1.3
65+	Place	100	2.5	7.9	7.9	62.6	19.2
	Dwelling	100	9.0	24.8	18.4	45.5	2.2

Source of duration-in-dwelling data: *Current Population Reports*, Series P-20, No. 47, Sept., 1953.

Table 1. Duration-of-residence in current place, 1958, and duration-of-residence in current dwelling unit, 1952. Percentage distribution by age.

duration of residence of less than 1 year correspond with the mobility status category, movers. If all other survey procedures corresponded, these two figures should be equal. The durations, however, refer to length of continuous residence in places, whereas the category of movers includes all local movers as well as migrants between places. The subdivisions of movers into same-county and different-county does not make complete equivalence possible. The residence history schedule calls for all moves between counties to be reported. In addition, some moves within counties should be reported: any move between cities or between a rural residence and a city constitutes a change of place. The number of persons with a duration less than one year would be expected to be intermediate between the numbers of same-county and different-county movers.

Table 2 reveals that durations of less than one year are less frequent than either same-county or different-county moves. The duration data, however, are similar both in magnitude and

in the patterning by age to the mobility data. Considering the wide divergence in survey questions, the differences between the two sets of data are not surprising. The inference that the less-than-one-year-duration data represent an undercount is plausible if three features of the survey procedures are noted. The Residence History Schedule emphasized "places where you have lived one year or longer," thus perhaps encouraging an overstatement of some durations. Secondly, the query for length of *continuous* residence may have been answered sometimes in terms of total life-time residence in the place, even if discontinuous. Thirdly, the Schedule requires the respondent to specify both when and where he has lived previously, whereas the one-year-mobility question requires recall only of residence at a specified prior time. Further quality checking of these data must await additional tabulations.

In a United Nations Seminar paper, Bogue has discussed the relative merits of several possible questions on migration. (7) As an alternative, rather than a supplement, to other approaches, a main function of duration data would be to permit estimates not only of current migration, but to permit "rough measures to be made of comparative differences in rates of in-migration in past years. . . ." Coupling the duration question

Table 2. Duration-of-residence in current place, 1958, and residential mobility, 1957–1958. Percentage distributions by age.

	18+	18–44	45–64	65+
Duration				
All Durations	100	100	100	100
More Than 1 Year	94.7	92.7	97.0	97.5
Less Than 1 Year	5.3	7.3	3.0	2.5
Mobility				
All Classes	100	100	100	100
Non-Movers	80.0	72.7	88.4	90.2
Movers, Same County	12.8	16.9	8.0	7.0
Movers, Different County	7.2	10.4	3.7	2.7

Source of mobility data: *Current Population Reports*, Series P-20, No. 85, Oct., 1958.

with a question on previous place of residence in a nationwide survey would permit estimates of out-migration as well. These estimates, however, could only be rough. Any survey approach for estimating past mobility omits the moves of those who have not survived to the present, thus understating the amount of past mobility and distorting the pattern by age. In addition, data on duration only in current residence conceal any previous mobility of those with short durations. A person who moved 5 years ago and again 2 years ago is counted only for the 2 year duration; a move made 5 years ago is recorded only if no later move has been made. Residence history data, providing information on all prior residences, would be needed to permit direct estimates of the previous migration rates of those still alive.

For the United States, data only on duration at current place are more useful in other ways than estimating previous migration. When cross-classified with appropriate characteristics, duration data can serve a second function noted by Bogue, estimation of "the extent of migration adjustment and the type adjustment in the community of destination." The data thus far tabulated from the 1958 Survey do not permit an illustration of this approach. One illustration is provided by the Massachusetts Census analyst, who, however, assumed rather than demonstrated such a positive relation between duration of residence and adjustment to community institutions. Klineberg's study of the relationship between intelligence measurements of Negro children and duration of residence in New York City is a well known example of this approach. (8)

Duration data are useful for analyzing a variety of problems in addition to the adjustment of migrants. Goldstein's concern with the stability and continuity of the population of Norristown is an example. Duration-of-residence data permit an emphasis on both the mobile and the stable portions of the population. From the preliminary tabulations of the May, 1958, Survey, patterns of mobility and stability can be delineated for regions and sizes of communities by age, sex, and color.[4]

[4] The preliminary tabulations may differ slightly from the final tabulations.

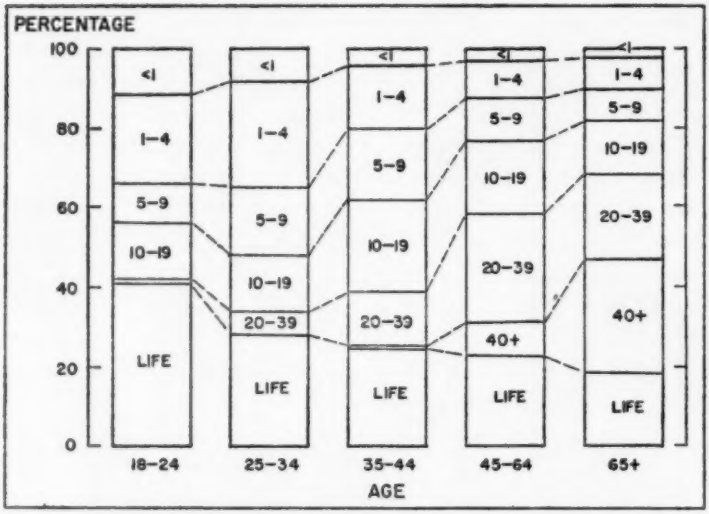

Fig. 1. Duration of residence in current place. Percentage with specified years or longer, by age, United States, 1958.

These preliminary data supplement the comparisons possible on the basis of annual migration rates, and permit additional inferences about migration patterns. Figures 1 through 6 and Table 3 portray the variation in durations of residence by these basic characteristics. These data illustrate the nature of duration-of-residence data and some of the ways of looking at them. Only a few features of these data can be noted here.

One of every four adults in the United States is reported as having lived his entire life in a single place. Any residential mobility for this one-fourth of the population has been local moving rather than intercommunity migration. Nearly one-half of the adult population has lived more than 20 years in the current place, and nearly two-thirds has durations of 10 years or more. Cumulating the proportions the other way emphasizes the extent of mobility rather than stability. One-fifth of adults has resided in the current place for fewer than 5 years, and one-third moved into their current place sometime during the last 10 years.

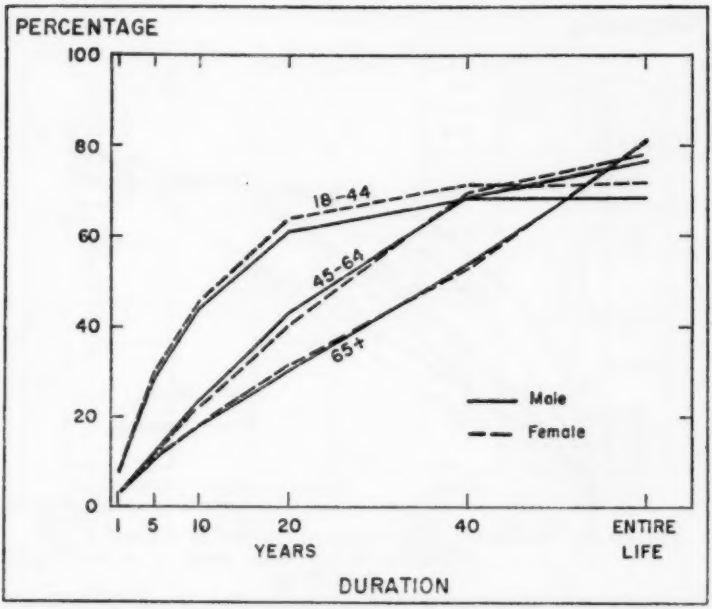

Fig. 2. Duration of residence in current place. Percentage with specified years or longer, by age and sex, United States, 1958.

In grouping durations, the "entire life" category does not fit precisely at one end of a continuum of years of residence since last move. A "life" duration for someone aged 18 is considerably shorter than a "40 years or more, but less than entire life" duration for someone aged 50. This problem is overcome in cross-classifying duration with age. In interpreting Figures 1, 2, and 3, it must be kept in mind that the "entire life" and "40 or more years" durations have different meanings for ages 18–44 than for the older ages.

The shorter durations for young adults do not reflect only their lesser opportunity for long durations because of their younger ages, but also the high mobility during early adulthood. At ages 18–24, two-fifths are still resident in their place of birth. This proportion drops sharply for ages 25–34, and declines gradually with further increases in age. The years of

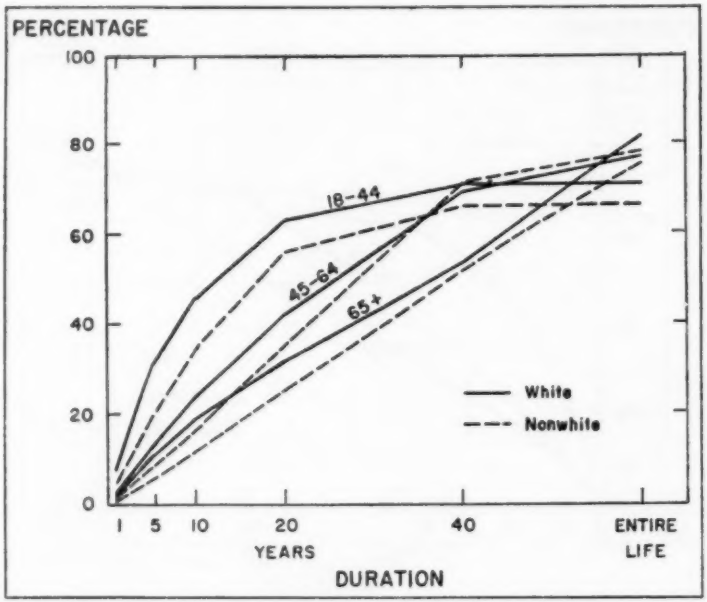

Fig. 3. Duration of residence in current place. Percentage with specified years or longer, by age and color, United States, 1958.

leaving home and establishing new families frequently involve changing the place of residence as well as the specific dwelling.

Durations of 20 or more years, but not embracing the entire life, increase sharply with age. Among persons 25–34, a duration of 20 or more years implies a move into the current place after birth but before age 14. Only 6 per cent of persons aged 25–34 fall into this group. Similarly, only 13 per cent of those aged 35–44 moved into their current places after birth but at least by age 24. These data suggest that relatively few persons change their residence between birth and late adolescence, whereas by the mid-twenties two-thirds have left their birthplaces.

Durations for the older age groups suggest that these persons settled down in their late twenties or early thirties, and were unlikely to change their place of residence thereafter. Local

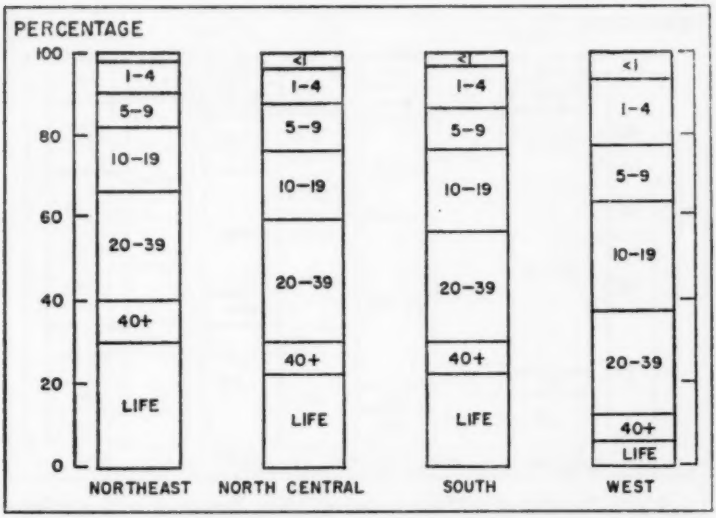

Fig. 4. Duration of residence in current place. Percentage with specified years or longer, by region, whites aged 45 to 64, 1958.

moving may have continued, and it is probable that many of the shorter durations for these persons reflect a recent move to the suburbs rather than a long-distance migration.

The differentials by sex, illustrated in Figure 2, are not large. Women aged 18–24 years not only have higher 1 year mobility rates, but higher rates for the previous 1–5 years. At these ages, men are much more likely to have spent 10 or more years, including entire life, in their current place. At ages 25–34, however, men have higher percentages with both short (less than 5 years) and long (life) durations. Among older persons, men have slightly higher proportions than women among the long durations categories, reflecting perhaps a greater likelihood of the wife moving to the husband's place of residence than of the husband moving to the wife's place. Classification by marital status would permit testing of the plausible inference that the duration patterns reflect age differentials at marriage and residence patterns after marriage.

The higher mobility of whites is reflected in Figure 3, which

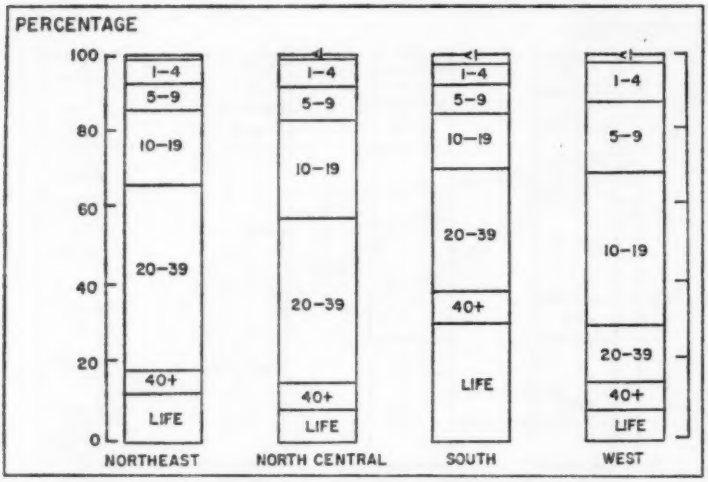

Fig. 5. Duration of residence in current place. Percentage with specified years or longer, by region, nonwhites aged 45 to 64, 1958.

shows generally longer durations for nonwhites. The duration data permit more interesting comparisons by color when classified by region, as in Figures 4 and 5. In the South, nonwhites aged 45–64 show much more residential stability than do whites. In the Northeast and North Central Regions, the duration data clearly reflect the heavy in-migrations of Negroes in the last 40 years. As compared to the whites in the regions, few of the nonwhites have lived their entire lives in a single place. Nonwhites are heavily concentrated in the 10–40 year durations. Perhaps the last change of place for many nonwhites is the move from the South to a Northern metropolis; once there, further migration is unlikely. These differentials between whites and nonwhites are apparent also in Figure 6, comparing durations for persons currently living in metropolitan places with durations for those in nonmetropolitan places.

In Table 3, places of current residence are further subdivided into size classes. For both whites and nonwhites, the highest proportion of life durations is found among farm residents. For whites, life durations in the largest cities are nearly as common

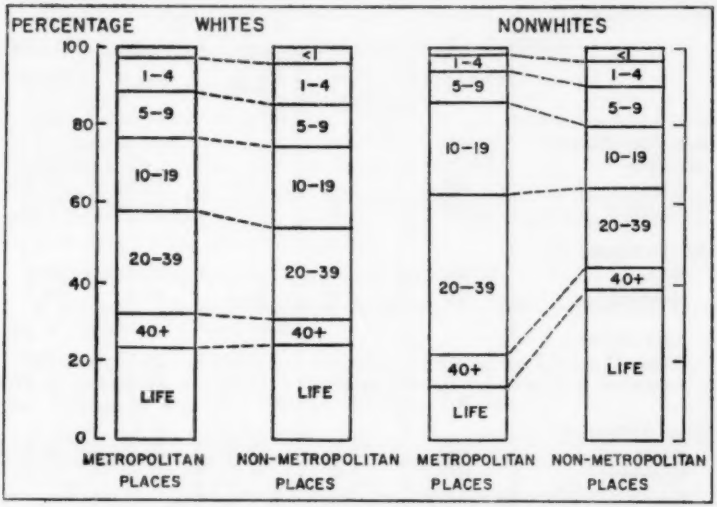

Fig. 6. Duration of residence in current place. Percentage with specified years or longer, by color and type of place, males aged 45 to 64, United States, 1958.

as in farm areas, and durations of more than 20 years are more common. Relatively few nonwhites, however, have lived their entire lives in any nonfarm places. In the larger metropolitan places, nonwhites much more frequently than whites have durations of 20 years or more, but less than life, reflecting both the timing of periods of urban in-migrations and the lesser total residential mobility of nonwhites.

Duration-of-residence data can contribute to our knowledge of migration differentials by age, sex, and other characteristics. They can be used to further document and analyze historical migrations, such as those of nonwhites to Northern metropolises. They permit analysis of population stability and mobility by regions and by types and sizes of places of current residence. The most distinctive feature of duration data, however, is the glimpse they give into migration as part of the life history of persons. An individual's changes of residence are not independent of previous changes of residence; neither are the migrations of a given year independent of the changing residential patterns

	All Durations	Duration in Years			
		Less than 5	5–19	20+	Entire Life
Metropolitan Places 500,000+					
White	100	5.2	17.5	39.8	37.5
Nonwhite	100	4.0	30.6	54.0	11.4
50,000–500,000					
White	100	8.6	28.4	41.1	21.9
Nonwhite	100	6.7	30.6	48.6	14.1
2,500–50,000					
White	100	18.4	45.7	26.2	9.7
Nonwhite	100	10.7	38.7	44.3	6.3
Rural Nonfarm					
White	100	18.5	39.8	24.8	16.9
Nonwhite	100	9.0	37.5	27.9	25.6
Non-Metropolitan Places 2,500–50,000					
White	100	15.9	34.1	34.6	15.4
Nonwhite	100	9.9	36.6	35.6	17.9
Rural Nonfarm					
White	100	18.1	34.8	27.2	19.9
Nonwhite	100	12.8	32.8	21.0	33.4
Rural Farm					
White	100	8.3	23.2	27.7	40.8
Nonwhite	100	6.6	13.9	18.9	60.6

Table 3. Duration-of-residence in current place. Percentage distribution by color and type and size of current place, males aged 45–64, United States, 1958.

of the nation. A single question on duration in current residence can provide but a small proportion of the data needed to proceed very far with the longitudinal analysis of migration. A second question, on place of previous residence, is necessary to permit duration analysis of specific migration streams. More questions are necessary to provide more complete longitudinal data. Analysis of the basic duration data continually suggests the need for such additional information. Duration-of-residence analysis is but a preliminary step in the systematic study

of migration within the context of the life cycle of the individual and the population redistributions of the nation.

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LENGTH OF THE FERTILE PERIOD

ROBERT G. POTTER, JR.[1]

INTRODUCTION

IT is well known that a woman is not equally fertile throughout her menstrual cycle. Only during a relatively short period, approximately in the middle of her cycle, does she have an appreciable chance of conceiving. The average duration of this "fertile period" is not known with precision. Yet such knowledge is important in order to be able to specify the relationships of coital frequency to ease of conception or to risk of contraceptive failure. For example, if the fertile period averages 24 hours, then doubling the rate of coitus might approximately double the monthly chance of pregnancy. In contrast, if the fertile period averages 72 hours, or even 48 hours, doubling a coital rate will fall well short of doubling pregnancy chances because of the heightened likelihood that two or more copulations will coincide with the same fertile period. As a second example, in the practice of artificial insemination by donor, it is common procedure to inseminate several times per menstrual cycle at 48 hour intervals. This interval is entirely reasonable if the fertile period lasts 48 hours, but is not short enough if the fertile period lasts only 24 hours.

The most direct approach to estimating the length of the fertile period, and the basis of most estimates, is to measure the useful life of spermatozoa and ova within the female reproductive tract. But such are the difficulties of measurement that published estimates have ranged from 72 hours down to less than 24.[2] Most investigators now doubt that the fertile period averages as long as 72 hours. Yet despite three decades of interest in the subject, it remains unsettled whether the fertile period averages closest to 12, 24, 36 or 48 hours.

[1] Office of Population Research, Princeton University. The writer is indebted to W. D. Borrie, A. J. Coale, P. C. Sagi, and C. Tietze for their valuable criticisms.

[2] For an early compilation of estimates, *see* Pearl, Raymond: NATURAL HISTORY OF POPULATION. London, Oxford University Press, 1939, p. 67.

Two investigators, Farris[3] and Tietze,[4] have used more indirect approaches. Following distinct lines of attack, they have independently estimated that the fertile period is 24 hours or less.

This paper has three objectives. First, results from studies of the longevity of sperm and ova within the female reproductive tract are briefly reviewed. Second, the focus is shifted to more indirect approaches with special attention paid to Tietze's scheme of analysis. Finally, Tietze's scheme of analysis is applied to two additional types of data.

Direct Approach

Most published estimates of the length of the fertile period have their origin in efforts to measure the periods during which ova remain fertile and spermatozoa retain their virility within the female reproductive tract. Fairly firm evidence exists that the ovum is typically fertilizable for less than 12 hours after ovulation.[5] This period being so brief, the length of the fertile period comes to depend pretty much on the duration of sperm virility within the female. Unfortunately this duration is not known at all precisely and cannot be measured directly. The only practical method of measurement is the period during which spermatozoa continue to show movement, at various sites in the female; but the period of motility is believed to exceed substantially the period of virility, though the precise extent of the differential is conjectural.

[3] Farris, Edmond J.: Human Fertility and Problems of the Male. White Plains, The Authors' Press, 1950, p. 191.

[4] Tietze, C.: Probability of Pregnancy Resulting from a Single Unprotected Coitus. *Fertility and Sterility*, September–October, 1960, xi, pp. 485–488. This paper is perhaps the first statistical study devoted entirely to the problem of estimating the length of the fertile period.

[5] Rock, J. and Hertig, A. J.: The Human Conceptus during the First Two Weeks of Gestation. *American Journal of Obstetrics and Gynecology*, 1948, 55, pp. 6–17. E. Potter interprets the research of Hertig and Rock to mean that "the normal life of the ovum after expulsion from the ovary is limited to 8 hours. After that degenerative changes take place and even though the ovum is fertilized, abortion or malfunction is the usual outcome." Pathology of the Fetus and the Newborn. Chicago, The Year Book Publishers, 1952, p. 4. After surveying the literature, Rubenstein *et al.* conclude: "the fertilizable life of the ovum is probably less than 6 hours." *See* Rubenstein, E. B.; Strauss, H.; Lazarus, M. L.; and Hankins, H.: Sperm Survival in Women. *Fertility and Sterility*, Jan.–Feb., 1951, 2, p. 15.

It is generally agreed that the cervix constitutes a particularly favorable site for sperm longevity. According to the researches of Cary,[6] Cohen and Stein,[7] and Moench,[8] sperm survival in the cervix may be put at about 48 hours, though much longer durations are reported as exceptional occurrences. Data pertaining to sperm survival in the uterus or in the oviduct are much more fragmentary. Belonoschkin summarizes the literature in the following way:

> Spermia exhibit approximately the following life spans in the various sections of the genitalia: in the vagina, 2 to 4 hours; in the cervix, as long as 72 hours; and in the cavum uteri about 24 hours. The life span in the tubes has not yet been accurately determined; it probably amounts to 48 hours.[9]

Thus it appears that 48 hours may be regarded as a liberal upper bound for the useful life of spermatoza within the female. If, in addition, the fertility of the ovum lasts only a few hours, toward which consensus now leans, then the fertile period cannot typically endure as long as 72 hours. Indeed doubts are raised about its averaging even 48 hours. However whether the fertile period averages closest to 12, 24, or 36 hours remains quite conjectural. Additional evidence is required for a judgment here.

Two Indirect Approaches

Farris and Tietze utilize more indirect methods to gauge the length of the fertile period. Farris derives an estimate of 12 to 24 hours from his experience with artificial insemination by donor.[10] Among patients successfully inseminated, he achieves

[6] Cary, W. H.: Duration of Sperm Cell Migration and Uterine Secretions. *Journal of the American Medical Association*, 1936, 106, p. 2222.

[7] Cohen, M. R. and Stein, I. F.: Sperm Survival at Estimated Ovulation Time. *Fertility and Sterility*, Jan.–Feb., 1951, 2, pp. 20–27; and by the same authors: Sperm Survival at Estimated Ovulation Time: Prognostic Significance, *Fertility and Sterility*, March–April, 1950, 1, pp. 170–175.

[8] Moench, G. L.: The Longevity of the Human Spermatozoa. *American Journal of Obstetrics and Gynecology*, 1939, 38, pp. 153–155.

[9] Belonoschkin, B.: Determination of the Fertilizing Ability of Sperm. *International Journal of Fertility*, Jan.–March, 1959, p. 7.

[10] Farris, Edmond J.: Human Fertility and Problems of the Male. White Plains, The Authors' Press, 1950, p. 191.

a pregnancy rate of .55 when inseminations are performed on the "correct" day as determined by the rat hyperemia test, a relatively exact technique for indicating time of ovulation. The high pregnancy rate of .55 falls away to .00 and .20 when inseminations are performed one day early and one day late.[11] However Farris' results are not to be taken at face value. Most of the patients inseminated 24 hours early or late are patients who have failed to conceive during two or more cycles of insemination performed at supposedly correct times and for this reason may be suspected of subfecundity.[12]

Recently Tietze, too, has estimated that the fertile period averages 12 to 24 hours.[13] To derive his estimate, Tietze brings together data pertaining to coital frequency and speed of conception. Since his procedure offers a point of departure for developing several alternative estimates, it is worth describing in detail. Before this description, however, it is convenient to distinguish additional aspects of the fertile period besides its average length.

Some Dimensions of the Fertile Period

One must exercise care in defining what is meant by the average length of the fertile period. Theoretically in any ovulatory cycle there is a point in time, some number of hours before or after ovulation, when coitus has it greatest chance of leading to conception. As the time of coitus deviates from this optimum, the probability of conception decreases. The curve describing this decline might be termed the "shape" of the fertile period. The area under this curve defines the "length" of the fertile period, which varies from month to month for the same couple, and of course among couples. Another important as-

[11] Potter, Jr., R. G.: Farris' Formula for Predicting Fertile Days. *In* Cold Spring Harbor Symposia on Quantitative Biology, Volume xxii, 1957, pp. 178–180. In this experience, 100 pregnancies are achieved in the course of 326 inseminations. The .55 rate refers to frequency of pregnancies during the initial 2 months. As will be discussed later, this rate of .55 is inflated by a tendency for patients to abandon treatment after a few months of unsuccessful insemination.

[12] *Ibid.*, pp. 183–185.

[13] Tietze, *op. cit.*

pect, and one often overlooked, is the proportion of menstrual cycles during which there exists even a possibility of initiating a detectable pregnancy. During many menstrual cycles such a possibility does not exist: the couple are constrained from intercourse by illness or temporary separation; the cycle is anovulatory; the particular ovum is incapable of fertilization; abortion occurs so early that conception is not recognized; and so forth. During these "unfavorable"menstrual cycles, one or more conditions make it impossible for any timing of coitus to lead to an identifiable conception.

By and large, when indirect methods of estimation are used, it is not possible to infer the average length of fertile periods without first making assumptions about other aspects, such as typical shape, variation in length, and typical frequency of unfavorable menstrual cycles. Problems of estimation are greatly simplified if one assumes that the fertile period is rectangular in shape, with all the hours of the menstrual cycle classified as either sterile or fertile. Then the length of the fertile period is simply the number of hours, during a favorable menstrual cycle, when the probability of conception is nonzero. Estimation is still further simplified by assuming that the fertile period is constant in length.

Tietze's Estimate

Tietze seeks to determine the range of fertile period length for which data on coital frequency remain consistent with data on monthly chances of pregnancy in the absence of contraception. Assumptions about coital frequency are based on figures reported for the female sample of Kinsey *et al.*[14] The mean monthly chance of conception in the absence of contraception Tietze assumes to be between .2 and .3.[15] He posits a constant

[14] Kinsey, A. C.; Pomeroy, W. B.; Martin, C. E.; and Gebhard, P. H.: Sexual Behavior in the Human Female, Philadelphia, W. B. Saunders, 1953, Table 93.

[15] The reasons which Tietze advances for choosing a range of .2 to .3 are not altogether convincing. He justifies the lower limit of .2 "mainly on the distribution of intervals between marriage and first birth, and between successive births within the same family, in a carefully studied rural population in the parish of Crulai,

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intermenstrum of 25 days. This intermenstrum is divided into two subperiods: a fertile period of F days and a sterile period of 25–F days. In other words, the fertile period is assumed constant in length and rectangular in shape. Furthermore every menstrual cycle is viewed as favorable in the sense that one coitus during any part of the fertile period suffices for conception and the resultant pregnancy is always detected.

Two alternative assumptions are made about the manner in which coition is distributed over the intermenstrum; and corresponding to these assumptions are a pair of models originally proposed by Glass and Grebenik.[16] In the first model it is assumed that there is an equal chance of coitus taking place at any time during the intermenstrum. Therefore chances of a single coitus occurring outside the fertile period is (25–F)/25, while chances that n coitions will fail to initiate pregnancy are

$$Q(F, n) = \left(\frac{25 - F}{25}\right)^n$$

Normandy, during the period 1674–1742. . . ." The upper limit of .3 he bases on the pregnancy rate, during the first month after deliberately stopping contraceptions, of two groups of urban Americans, totalling 2,677 couples for which combined sample he calculates, in another paper (viz., Differential Fecundity and Effectiveness of Contraception. *The Eugenics Review*, January, 1959, 50, p. 231) a pregnancy rate of .34.

Yet the range of .2 to .3 does find justification in a forthcoming analysis focused on problems of estimating mean fecundability; *see* Chapter IV and its accompanying appendix in Westoff, C. F.; Potter, Jr., R. G.; Sagi, P. C.; and Mishler, E. G.: FAMILY GROWTH IN METROPOLITAN AMERICA, to be published by Princeton University Press. According to the estimates judged most useful, the proportion of American couples becoming pregnant in the first month of marriage, when not using contraception, ranges from .25 to .30, while the proportion of pregnancies occurring the first month after deliberately stopping contraception ranges from around .30 to .40. Almost certainly these estimates are upwardly biased, in varying degree, as a result of insufficient pains taken to insure that only conceptions coinciding with first menstrual mid-periods after marriage, or after deliberate cessation of contraception, are included, while conceptions occurring during second menstrual mid-periods are excluded, even though many of them occur only 4 or 5 weeks after marriage or cessation of contraception. When allowance is made for this bias, the range of .2 to .3 appears more reasonable than .3 to .4, though the lower bound of .2 represents a firmer estimate than the upper bound of .3. The consistent tendency for the pregnancy rate to be higher the first month after deliberately stopping contraception, as compared to the first month of marriage before starting contraception, is attributed in the same analysis, to a net balancing of several measurement biases and selectivities with respect to fecundability. In sum, .2 probably underestimates the mean fecundability of urban Americans, while, less assuredly, .3 overestimates it.

[16] Glass, D. V. and Grebenik, E.: THE TREND AND PATTERN OF FERTILITY IN GREAT BRITAIN. Papers of the Royal Commission on Population, Vol. 6, London, H.M.S.O., 1954, Part I, p. 255.

In the second model, it is assumed that at most one coitus occurs in any 24 hour span. Hence chances of n coitions not coinciding with the fertile period are

$$Q'(F, n) = \binom{25 - F}{n} \Big/ \binom{25}{n}$$

Let $P(F, n)$ equal $1 - Q(F, n)$ and $P'(F, n)$ equal $1 - Q'(F, n)$. It can be shown that $P'(F, n)$ is at least as large as $P(F, n)$, meaning that imposing a limit on the number of copulations per 24 hour span somewhat increases chances that at least one coitus will coincide with the fertile period. Thus the second model, which is probably the more realistic of the two, yields the higher pregnancy rates.

Tietze's problem reduces to one of finding the values of F which will generate monthly chances of pregnancy between .2 and .3 when n is assigned values corresponding to the mean coital frequencies of United States couples at reproductively important ages. Predicated on an intermenstrum of 25 days and the experience of Kinsey's female sample, the most relevant values for n range from 7 to 11 equivalent to rates of 2 to 3 times per week. F is successively assigned values of $\frac{1}{2}$, $\frac{3}{4}$, 1, $1\frac{1}{2}$ and 2, corresponding to assumptions that the fertile period is 12, 18, 24, 36 and 48 hours. On the basis of Glass and Grebe-

Table 1. Expected rate of conception during one menstrual cycle by coital frequency and number of hours during which fertile coitus is possible.

Coital Frequency per Cycle	Number of Hours per Cycle during which Fertile Coitus is Possible				
	12	18	24	36	48
4	.078–.083	.115–.122	.151–.160	.219–.232	.284–.300
5	.096–.104	.141–.153	.185–.200	.266–.287	.341–.367
6	.114–.127	.167–.185	.217–.240	.310–.341	.394–.430
7	.132–.150	*.192–.217*	*.249–.280*	.352–.393	.442–.490
8	.149–.173	*.216–.250*	*.279–.320*	.390–.443	.487–.547
9	.166–.198	*.240–.283*	.308–.360	.427–.492	.528–.600
10	*.183–.223*	*.263–.317*	.335–.400	.461–.540	.566–.650
11	*.199–.249*	*.285–.351*	.362–.440	.494–.586	.600–.697
12	.215–.276	.306–.386	.387–.480	.524–.630	.632–.740

nik's models, two fecundabilities (monthly probabilities of pregnancy) are calculated for each pair of F and n values. Tietze's results are duplicated in Table 1. Quite clearly, for the most appropriate coital frequencies, it is fertile periods of 12–24 hours that yield conception rates of .2 to .3, while longer fertile periods, say 36 or 48 hours, yield excessively high estimates of fecundability.

Appraising Tietze's Estimate

As Tietze would be the first to emphasize, this approach contains a number of simplifying assumptions and biases. Before considering some of these biases, one cautionary remark should be made about Glass and Grebenik's second model, which uses the relationship

$$Q'(F, n) = \binom{25 - F}{n} \Big/ \binom{25}{n}$$

This model is not really applicable unless F is an integer. When the length of the fertile period is an integral F days, so that the intermenstrum divides into F fertile days and 25–F sterile days, one can enumerate events in a clear enough fashion. For example, there are $\binom{25 - F}{n}$ ways of distributing n coitions among the 25–F sterile days without more than one coitus to a day, just as there are $\binom{25}{n}$ ways of distributing n coitions among the full 25 days of the intermenstrum.

But suppose that the fertile period is 12 or 18 or 36 hours. Following Tietze, one can assign values of $\frac{1}{2}$, $\frac{3}{4}$ and $1\frac{1}{2}$ to F and obtain numerical answers from the formula for $Q'(F, n)$. However, it is no longer clear what situation is being represented. The enumeration of events has become ambiguous. A more elaborate model is needed to handle these fractional values of F.[17] Because of this problem, the second model of Glass

[17] For example, one might assume that the intermenstrum is divided into 25 days; that no more than one coitus occurs during any one day; and that the particular hour of coition within a day is random. Suppose further that the fertile period is less than 24 hours and that its length of s hours falls entirely within one day.

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and Grebenik will not be used, in later sections of this paper, except in connection with fertile periods of 24, 48, or 72 hours length. Fortunately, fractional values of F do not present a problem for the first model of Glass and Grebenik.

Turning to the question of biases inherent in Tietze's approach, one of these biases works toward an exaggeration of fertile period length.[18] Some couples deliberately increase their coital frequency during that part of the menstrual cycle which they believe to be most fertile. It is not known what proportion of couples in the United States have accurate information about the positioning of the fertile period in the menstrual cycle or what proportion, having this knowledge, use it to regulate their intercourse when trying to become pregnant. If this proportion is appreciable, then the average fecundabilities of .2

Then the probability of a coitus coinciding with the fertile period is $(s/24)P'(1,n)$. This follows since $P'(1,n)$ represents the probability of a coitus coinciding with the day containing the fertile period and given that event, the probability that the coition will coincide with one of the s fertile hours is s/24. Fecundability values obtained in this manner, with s set equal to $\frac{1}{2}$ and $\frac{1}{4}$, prove barely lower than those obtained by Tietze when he assigns values of $\frac{1}{2}$ and $\frac{1}{4}$ to F in the formula for $Q'(F,n)$. Hence the qualification probably has little substantive importance.

The above logic may be adapted to handle fraction values of F between 1 and 2, but the calculation of fecundabilities becomes more tedious and does not produce unique results unless the position of the fertile period relative to the grid of 24-hour spans is made rigid.

[18] One simplifying assumption implicit in Tietze's approach, namely that heightened coital frequency does not adversely affect male virility, appears warranted for most males, except perhaps when very high frequencies are involved. In a series of articles published in *Fertility and Sterility*, J. MacLeod and R. Z. Gold have shown, in a convincing way, that sperm count is a secondary factor except when it falls below a minimum, estimated to be in the neighborhood of 20 million sperms per c.c. or 60 million total. Given a sperm count above this minimum, the important factors for virility—among those few factors measurable in large samples—become the percentage of active sperms and the character of their movement. Heightened coital frequency does not appear to penalize either quality. Furthermore, coital frequencies of 3 or 4 times per week do not depress the sperm counts of most males below, or even near, critical levels. Of special relevance, among several pertinent articles, is "The Male Factor in Fertility and Infertility: Semen Quality in Relation to Age and Sexual Activity." *Fertility and Sterility*, January–February, 1953, 4, pp. 10–33. For the oligospermatic male who barely meets, or fails to meet, the minimum sperm count even after several days of continence, increases from moderate to high coital frequencies may lower conception chances. *Cf.* Farris, Edmond J.: HUMAN FERTILITY AND PROBLEMS OF THE MALE, pp. 101–119. The incidence of oligospermatic males in the general population is not known. MacLeod and Gold find that 7 per cent of the husbands from 936 fertile unions have total sperm counts below 50 million while the corresponding frequency among husbands from 783 infertile unions is 15 per cent: Spermatozoon Counts in 1,000 Men of Known Fertility and in 1,000 Cases of Infertile Marriages. *Journal of Urology*, 1951, 66, p. 439.

to .3 are being generated by shorter fertile periods than would otherwise be the case.

Most of the other biases appear to be working in the opposite direction, that is, they favor underestimation of the fertile period. On the basis of calculations, summarized in the Appendix, the tentative conclusion is that three of these downward biases are of secondary magnitude. They are biases arising from assumptions (1) that the fertile period is constant in length; (2) that it is rectangular in shape; and (3) that all couples have the same coital frequency, rather than frequencies varying around a stipulated mean.

However even if the judgment is correct that these listed biases are minor, there remains one reason for suspecting that Tietze's estimate of 12 to 24 hours is low. Tietze assumes that every menstrual cycle contains a fertile period of such character that one coitus during it suffices to initiate pregnancy and this pregnancy is always recognized. As noted already, many more conditions than an optimally timed copulation are required to produce an identifiable gestation. The male partner must be able to deposit sperm of sufficient volume and quality. The menstrual cycle must be ovulatory. Upon ovulation, the extruded ovum must reach the Fallopian tubes and from there, fertilized, it must pass to the uterus, implant, and endure long enough for pregnancy to be detected. If the percentage of unfavorable cycles, lacking one or more of these prerequisites, is small, then the fertile period may be as short as Tietze estimates it to be. However, if the percentage of unfavorable menstrual cycles is one half or more, then the fertile period probably averages nearer 36 hours than 18.

Unfortunately the frequency of unfavorable cycles is not known within a wide range. The incidence of seriously subfertile husbands is probably quite low, at least in samples of couples who are demonstrating their fertility by having another pregnancy. Presumably too, the proportion of menstrual cycles during which illness or temporary separation compel continence is fairly low. The rate of anovulatory cycles is usually put at

around 5 per cent, and higher for subfecund women.[19] How frequently accidents befall ova between ovaries and Fallopian tubes is unknown.[20] It is thought by some experts that many ova reaching the tubes are incapable of fertilization, though a quantitative estimate of their frequency is not available.[21]

However, of all the factors contributing to unfavorable menstrual cycles, perhaps the most important is early foetal wastage. Numerous studies indicate that 10 per cent of all recognized pregnancies end in spontaneous abortion, with the highest wastage rates experienced in the second and third months of pregnancy.[22] It is generally believed that the true wastage rate is highest in the first month and appears lower only because of the difficulty of detecting early miscarriages. It is also generally agreed that the majority of early foetal deaths are attributable to constitutional defects of the ovum and a lesser frequency

[19] Basal body temperature and endometrial biopsy have been the two means commonly used to measure incidence of anovulation. Though the two methods have given consistent results, the possibility that both are downwardly biased cannot be excluded. Several studies indicate frequencies below 10 per cent for regularly menstruating women in the 20's or early 30's. See the review articles: Wong, A.S.H.; Engle, E. T. and Buxton, C. L.: Anovulatory Menstruation in Women. *American Journal of Obstetrics and Gynecology*, 1950, 60, pp. 790–797, and Tompkins, P.: Endometrial Biopsy Determination of Incidence of Ovulation in 402 Regularly Menstruating Women. *Fertility and Sterility*, January–February, 1953, 4, pp. 76–79. Data showing that anovulation increases at either end of the reproductive span is given in Collett, M. E.; Wertenberger, G. E.; and Fiske, V. M.: The Effect of Age upon the Pattern of the Menstrual Cycle. *Fertility and Sterility*, September–October, 1954, 5, pp. 437–448. That frequent anovulation is also one symptom of subfecundity is documented by Rock, J.; Bartlett, M. K.; and Matson, D. D.: The Incidence of Anovulatory Menstruation among Patients of Low Fertility. *American Journal of Obstetrics and Gynecology*, 1939, 37, pp. 3–12.

[20] Whether or not this loss is consequential is debated in the following article and its accompanying discussion, Westman, A.: Investigations into the Transport of the Ovum. *In* Engle, Earl T. (ed.): Studies on Testis and Ovary Eggs and Sperm. Springfield, Ill., Charles C. Thomas, 1952, pp. 163–175.

[21] *See* Witschi, E.: Overripeness of the Eggs as a Cause of Twinning and Teratogenesis: A Review, *Cancer Research*, November, 1952, 12, pp. 763–786. Witschi makes much of the fact "that in all carefully investigated polyovular mammals at least one-third of ovulated eggs either are not fertilizable or produce grossly abnormal embryos," *ibid.*, p. 775. He also believes that the work of A. T. Hertig and J. Rock (cited below) proves that this generalization applies to the human female. *See* also the review article of L. B. Shettles: The Ovum in Infertility, Abortion, and Developmental Anomaly. *Fertility and Sterility*, Nov.–Dec., 1956, 7, pp. 561–571.

[22] Foetal, Infant and Early Childhood Mortality, Vol. I. New York, United Nations, 1954, ST/SOA/Series A/13, pp. 14–16.

to deficiencies in the maternal environment.[23] One expert, reviewing the literature in 1954, concluded that "the total prenatal loss may be as low as 20 and as high as 70 per cent of all conceptions."[24]

Only one authoritative estimate exists of the incidence, among fertile women, of fertilized ova destined to abort. Over a 17 year period, Hertig and Rock have recovered 34 early conceptuses from 210 patients. Ten of the 34 fertilized ova, or approximately 30 per cent, have been interpreted as so abnormal as to run a high risk of aborting.[25]

The 34 conceptuses actually came from a smaller group of 107 patients who satisfied three conditions making it much more likely that fertilized ova would be recovered. First, each of the women gave evidence of having ovulated during the menstrual cycle in which the operation occurred. Second, each reported having intercourse within 24 hours before or after ovulation as judged from the endometrial morphology. Third, all these women appeared free of pathological conditions in the tubes, ovaries, or uterus that would interfere with conception. In addition, all had previous pregnancies. Their ages, ranging from 25 to 43, averaged 33 years, and, more important, the 24 women producing normal ova averaged about the same

[23] In 3 studies, the proportions of early abortions ascribed to "defective germ plasm" are .85, .63, and .66, based on sample sizes of 104, 979, and 791 respectively: *ibid.*, p. 16. See also Corner, G. W. and Bartelmez, G. W.: Early Abnormal Embryos of the Rhesus Monkey. *In* Engle, E. T. (ed.): PREGNANCY WASTAGE. Springfield, Ill., Charles C. Thomas, 1953, pp. 3–8.

[24] FOETAL, INFANT AND EARLY CHILDHOOD MORTALITY. Vol. I, p. 1.

[25] Thirteen of the 34 ova, or 38 per cent, are considered abnormal in some degree or other. *See* Hertig, A. T.; Rock, J. and Adams, E. C.: A Description of Human Ova within the First 17 Days of Development. *American Journal of Anatomy*, 1956, 98, p. 438. Ten of the 34 early conceptuses appear destined for abortion, with or without clinical signs of pregnancy. *See* Hertig, A. T.; Rock, J.; Adams, E. C. and Menkin, M. C.: Thirty-Four Fertilized Ova, Good, Bad, and Indifferent, Recovered from 210 Women of Known Fertility. *Pediatrics*, January, 1959, 23, p. 205. Based on a somewhat smaller experience of 28 early conceptuses recovered from 136 patients, the same investigators interpreted 12 ova (43 per cent) as abnormal in some degree, of which 7 ova (25 per cent) seemed so abnormal as to be certain of aborting. These 7 they subclassified into 4 (14 per cent) liable to abort without clinical signs of pregnancy and 3 (11 per cent) liable to abort with pregnancy manifest. *See* Hertig, A. T. and Rock, J.: A Series of Potentially Abortive Ova Recovered from Fertile Women Prior to Their First Missed Menstrual Period. *American Journal of Obstetrics and Gynecology*, 1949, 58, p. 986.

age (33.8 years versus 33.1) as the 10 women producing abnormal ova.[26]

Among the 107 patients, one factor greatly affecting chances of recovering an ovum was the stage of development of that ovum at the time of operation. Chances of recovery are slim while the ovum is still in the tubes or during the first 2 or 3 days of implantation. Chances are higher during a brief period when the ovum is free in the uterus, just prior to implantation. Recovery becomes relatively assured only when the ovum is well implanted.[27] Four of 8 tubal ova proved abnormal, but such a small sample does not yield trustworthy inferences. Thirty-six of the patients were operated upon late enough in the menstrual cycle so that theoretically a fertilized ovum had time to become well implanted if it was going to. From these 36 women, 21 early conceptuses were collected. Six of the 21 ova appeared fated to abort, a rate of foetal wastage of 28.6 per cent.[28] This wastage rate does not include fertilized ova failing to implant. Hence the total rate of foetal wastage may exceed 30 per cent. However this conclusion is uncertain because the lower bound of 28.6 per cent, based on only 21 cases, is subject to a large sampling error.[29]

In view of all these factors that can prevent the initiation of an identifiable pregnancy during a particular menstrual cycle —forced continence, anovulation, lost ova, failures of fertilization, and early foetal wastage—it is unlikely that the incidence of unfavorable menstrual cycles is less than twenty per cent and may be as high as 50 per cent or more. In brief, as stated at the outset, the frequency of unfavorable menstrual cycles is not known within a wide range. Tietze's estimate of 12–24

[26] Hertig and Rock, Thirty-Four Fertilized Ova . . . , *Pediatrics*, January, 1959, 23, pp. 204–205.

[27] *Ibid.*, pp. 204–206.

[28] *Ibid.*, p. 206.

[29] Given random samples of this size, one can expect to observe, about once in 40 times, a rate of .286 or higher even though the population rate is only .14 per cent. Under the same sampling conditions, one may expect, about once in 40 times, to observe a rate of .286 or more even though the population rate is .50 per cent. These proportions have been derived by setting $p+2(pq/21)^{\frac{1}{2}}$ and $p'-2(p'q'/21)^{\frac{1}{2}}$ equal to .286 and solving for p and p'.

hours as the length of the fertile period is correspondingly uncertain. Possibly the fertile period is 18 hours or less if the proportion of unfavorable menstrual cycles is something like one-fifth or one-quarter and if an important fraction of United States wives possess, and use, accurate information about the positioning of the fertile period within the menstrual cycle. Possibly too the fertile period is nearer 36 hours if deliberate timing of intercourse has only secondary importance and if the fraction of unfavorable menstrual cycles exceeds one-half. Clearly, additional data are needed to settle whether the fertile period averages nearer 18 or 36 hours.

Experience with Artificial Insemination by Donor

Additional evidence comes from the practice of artificial insemination by donor. Before considering the experience of E. J. Farris, attention will be given to reports by five physicians: A. F. Guttmacher, J. O. Haman, S. J. Kleegman, L. Portnoy, and F. C. Shields. These physicians, who perform several inseminations per menstrual cycle, at 48 hour intervals, start these inseminations early enough and continue them long enough to be confident of bracketing the fertile period.[30] This practice of multiple inseminations is made necessary by the unreliability of available techniques for dating ovulation.

Of interest is the proportion of fecund patients who become pregnant during the first month of treatment when inseminations are performed at 48 hour intervals. This figure cannot be estimated directly, though two calculations yield upper and lower bounds for it. In the five series combined, the proportion of pregnancies occurring in the first month of insemination is .39, based on 374 pregnancies, with an approximate standard error of .025. This proportion may be interpreted as an overestimate of the figure desired because of a tendency for patients to drop out after a few months of unsuccessful treatment, so that only patients who become pregnant fairly promptly are

[30] These five series and two others are compared in Potter, Jr., R. G.: Artificial Insemination by Donors. *Fertility and Sterility*, January–February, 1958, 9, pp. 37–53.

included in the calculation. Alternatively, when all 534 patients are taken as the base, 27 per cent become pregnant in the first month of insemination. This proportion, with an approximate standard error of .019, affords an underestimate inasmuch as some of the patients are sterile.

In the five series under review, then, the mean fecundability of the nonsterile patients may be estimated as between .27 and .39. If the fraction of sterile patients is small, as seems likely, then the correct value is close to .27. Almost certainly it is well under .39, say .33 or less, because of the many patients who drop out after a few months of treatment.[31]

For the sake of illustration, accept .3 as a provisional estimate of the mean fecundability of patients inseminated every 48 hours. Still one cannot draw inferences about the length of the fertile period without first assuming something about the frequency of unfavorable menstrual cycles. If this incidence is taken as 20 per cent, probably a low estimate, then one must posit an 18 hour fertile period, derived from the equation

$$(x/48)\ .8 = .3$$
$$x = 18.$$

Alternatively, if one assumes that half or more of all menstrual cycles are unfavorable, then one must postulate a fertile period

[31] Only Kleegman's report contains full information about patient drop-out. Of 116 patients, 42 fail to become pregnant and of these latter, 28 have abandoned treatment by the end of the 4th month. Clearly, if all her patients had been willing to continue treatment for a year, if necessary, the proportion eventually becoming pregnant might have been considerably higher than the 64 per cent observed. This conclusion is reinforced by the fact that the three physicians who mention early patient loss as a problem—namely, Guttmacher, Kleegman, and Portnoy—succeeded in impregnating only .55 to .68 of their patients, whereas the other two physicians, Haman and Shields, report proportions of .76 and .78.

It is plausible but not demonstrable that the fraction of sterile patients is low in the five series. Theoretically, a wife is not accepted for treatment unless her husband is found sterile and she herself appears capable of bearing a child. If prognosis of the husband as sterile could be regarded as always reliable, then one could reasonably infer that the wife, despite her history of infertility, has no greater chance of being sterile than a woman of her age in the general population; and this chance of sterility is quite low for women in their twenties and early thirties. However, in unknown degree the tests performed on the husbands are misleading. Further, the standards of fitness required of the patients themselves vary greatly from one practice to another. It is not even certain that all the donors are virile, precautions notwithstanding.

of 30 hours or more. This range of 18 to 30 hours is somewhat high or low depending on whether the mean fecundability of patients inseminated every 48 hours is below or above .3. In sum, these results based on five series of artificial inseminations, by donor corroborate, but do not extend, the results obtained by Tietze.

Additional implications about the length of the fertile period, and also about the incidence of unfavorable menstrual cycles, are gained by considering a sixth series accumulated by Farris. In this series at most one insemination is performed per menstrual cycle, with this insemination timed by his relatively precise rat hyperemia test. (Since this technique of dating ovulation requires a special colony of rats, it is not practical for the physician.) No insemination is performed during a month when the patient exhibits certain patterns of hyperemic reaction. Farris claims that past experience has shown that these patterns are incompatible with pregnancy. Thus Farris may have a means of avoiding useless insemination during some of the unfavorable menstrual cycles.[32]

On the basis of 232 inseminations, nearly all of them representing first or second months of treatment, performed on successfully treated patients, Farris and his coworkers achieved 128 pregnancies, for a pregnancy rate of .55.[33] Although his pregnancy rate during first months of insemination cannot be

[32] Two articles containing description of Farris' procedures are his: A Test for Determining the Time of Ovulation and Conception in Women. *American Journal of Obstetrics and Gynecology*, 1946, 52, pp. 14–27 and The Prediction of the Day of Human Ovulation by the Rat Test as Confirmed by 50 Conceptions, *ibid.*, 1948, 56, pp. 347–352. *See* also relevant sections of his HUMAN OVULATION AND FERTILITY. Philadelphia, Lippincott, 1956. The most searching appraisal of the rat test is reported in Corner, G. W.; Farris, E. J.; and Corner, Jr., G. W.: The Dating of Ovulation and Other Ovarian Crises by Histological Examinations in Comparison with the Farris Test. *American Journal of Obstetrics and Gynecology*, 1950, 59, pp. 514–528. For additional comment, see Potter, Jr., R. G.: Farris' Formula for Predicting Fertile Days. COLD SPRING HARBOR SYMPOSIA ON QUANTITATIVE BIOLOGY, Vol. 22, 1957, pp. 176–185.

[33] In 1957, the writer estimated that on the basis of 154 inseminations, performed at estimated optimum time, Farris and his co-workers had produced 84 pregnancies: *op. cit.*, p. 179. Subsequently, in a personal communication, Dr. Farris reported 44 additional pregnancies preceded by 80 inseminations. For more data on a total experience of 162 conceptions by insemination, *see* Farris, E. J.: The Period of Human Ovulation and a Consideration of the Fertile and Infertile Periods. *Acta Endocrinologica Supplementum*, 1956, 28, pp. 114–120.

calculated exactly, presumably it is somewhat higher than .55.

The difference between a rate of .55 based on 128 pregnancies and one of .39 based on 374 is highly significant statistically.[34] Data are not available to estimate the proportion of Farris' patients who become pregnant the first month of insemination, to compare with the .27 calculated for the other five series. One might assume that the proportion of pregnancies occurring in the first month has the same ratio in Farris' practice to the proportion of patients becoming pregnant in one month of treatment as in the other five practices. That is, one might multiply Farris' pregnancy rate of .55 by (.27/.39) to obtain .38. Quite likely this estimate is low. Farris' loss of fecund patients through drop-out is relatively low if only because he achieves so many quick impregnations. The incidence of reproductive pathology may also be relatively high among Farris' patients, excepting comparison with Portnoy's sample.[35] Hence the proportion of Farris' fecund patients becoming pregnant in the first month is probably above .40 but several points below .55, say for purposes of discussion .4 to .5.

Now if the rat hyperemia test is as accurate a means of dating ovulation as its originator believes, then a pregnancy rate of .4 to .5 may approach the maximum possible, thereby implying an incidence of unfavorable cycles of around 50 to 60 per cent. This conclusion, if tempting, is risky. The rat hyperemia test is subject to error having a standard deviation of several hours at least; and to this error must be added the possibility of a several hour bias.[36] In addition, Farris and his coworkers cannot always arrange to have the time of insemination coincide with the time indicated as best by the rat test. On this ground, the maximal pregnancy rate might be well over .5. On the other hand, Farris withholds insemination in roughly one out of five cycles which appear unfavorable and by this means raises to an unknown extent his pregnancy rate. Despite these uncertainties, Farris' experience lends added plausibility

[34] The associated critical ratio exceeds 3.
[35] Potter, Jr., R. G.: Artificial Insemination by Donors, p. 40.
[36] Potter, *op. cit.*, pp. 178–179.

to the idea that the incidence of unfavorable cycles may be as high as one-half.

The fact that Farris obtains a higher pregnancy rate than do the five physicians inseminating at 48 hour intervals implies, plainly enough, that during a menstrual cycle the probability of conception does not remain near peak values for as long as 48 hours. In addition, the difference in pregnancy rates is consistent with, but does not prove, the hypothesis that the fertile period averages well under 48 hours.[37]

Conception Delays as Affected by Coital Frequency

The last type of data to be considered is the pregnancy rates of women reporting different coital frequencies, in the absence of contraception. As noted already, the results of MacLeod and Gold suggest that male virility is not ordinarily jeopardized by increased sexual activity except possibly when the male is oligospermatic or when the increase is to very high coital frequencies. Nevertheless there is one reason for not expecting increases in coital frequency to produce commensurate increases in fecundability. As coital frequency increases, so does the chance of 2 or more coitions coinciding with the same fertile period, with all but the first of this set of coitions rendered in some degree superfluous. Furthermore, the longer the fertile period, the more important this attenuating factor. Thus the extent to which coital frequency differentiates conception delays offers an additional clue as to the length of the fertile period.

For United States couples, only three sets of conception delays have been found that are classifiable by coital frequency. These three series are first reviewed. Next, under Tietze's simplifying assumptions, the models of Glass and Grebenik are used to compute hypothetical conception delays as differentiated by coital frequency. Finally, from the comparison of empirical and hypothetical values, implications are drawn about

[37] If one assumes that the fertile period is nearly rectangular in shape, then the implication of a length well under 48 hours follows. But other shapes can be stipulated which could give the observed difference in pregnancy rates even though the area under the curve defining conception chances totaled more than 48 hours.

Coital Frequency	Number of Pregnancies	Mean Conception Delay
2 ×/Week	51	8.4 Mos.
3	468	6.9
4	224	5.2
5 or More	57	4.5

Table 2. Mean conception delay as related to coital frequency: Stix data.

Source: Stix, R. K.: Birth Control in a Midwestern City, I. Milbank Memorial Fund *Quarterly*, January, 1939, 17, Table 6, p. 82.

the length of the fertile period and the frequency of unfavorable menstrual cycles.

Two of the sets of conception delays classifiable by coital frequency are reproduced in Tables 2 and 3. Stix's data, in Table 2, furnish the mean conception delays of women reporting frequencies of 2, 3, 4 and 5 or more times per week.[38] These women, who averaged 5 years of marriage and 4 pregnancies, represent white patients attending one of the contraceptive clinics under the auspices of the Cincinnati Committee on Maternal Health during the five year period 1929 to 1934. Those who did not practice contraception before their first pregnancy were asked for the number of months elapsing between marriage and pregnancy and for their coital frequency immediately after marriage. Stix excludes from her tabulation patients known to have gynecological pathology.

In Table 3 proportions conceiving in less than 6 months are compared among women reporting four different levels of

Table 3. Proportions conceiving in less than six months as related to coital frequency: MacLeod and Gold data.

Coital Frequency	Number of Women	Proportion Conceiving in 5 Months or Less
Under 2×/Week	133	.29
2 or 2½	123	.46
3 or 3½	99	.52
4 or More	72	.83

Source: MacLeod, J. and Gold, R. Z.: The Male Factor in Fertility and Infertility. *Fertility & Sterility*, January–February, 1953, 4, Table 19, p. 29.

[38] Stix, R. K.: Birth Control in a Mid-Western City; I. Milbank Memorial Fund *Quarterly*, January, 1939, 17, pp. 69–91.

sexual activity. MacLeod and Gold's sample of "fertile" couples represent couples using the antepartum clinic of the Lying-In Hospital, part of the New York Hospital-Cornell Medical Center.[39] These patients have never applied to hospital clinics or consulted private doctors because of an infertility problem. Furthermore, the pregnancy bringing them to the antepartum clinic is not their first.

The two tables confirm that a strong inverse relation exists between conception delay and reported coital frequency. Yet puzzling enough, this strong association is not substantiated in data published by Stix and Notestein for a group of patients attending the Birth Control Clinical Research Bureau in New York City during the years of 1931 and 1932.[40] Mean conception delay shows almost no variation among 4 levels of reported activity ranging from "once per week or less" to "7 times per week."[41] As in the Cincinnati study by Stix, the question about frequency of intercourse pertained to the period immediately following marriage, though some of the marriages took place as long as 20 years prior to interview. Thus the recall periods average longer in the investigation of Stix and Notestein. Still, it is hard to believe that this factor alone explains the anomalous absence of relationship between conception delay and coital frequency found in this one study.

Given Tietze's simplifying assumptions, one may use the two models of Glass and Grebenik to estimate hypothetical mean conception delays, or hypothetical proportions conceiving in less than 6 months, for any combination of coital fre-

[39] MacLeod, J. and Gold, R. Z.: The Male Factor in Fertility and Infertility: Semen Quality and Certain Other Factors in Relation to Ease of Conception. *Fertility and Sterility*, January–February, 1953, 4, pp. 10–33.

[40] Stix, R. K. and Notestein, F. W.: CONTROLLED FERTILITY. Baltimore, William and Wilkins Co., 1940, p. 34. Stix briefly discusses the lack of relationship in: The Medical Aspects of Variations in Fertility. *American Journal of Obstetrics and Gynecology*, April, 1938, 35, pp. 9, 10. G. W. Beebe reports "a small but reliable difference in the pregnancy rates for women reporting different coital frequency" in his Logan series. CONTRACEPTION AND FERTILITY IN THE SOUTHERN APPALACHIANS. Baltimore, William and Wilkins Co., 1942, pp. 79, 80.

[41] The mean conception delays are 4.6, 4.7, 4.3 and 3.7 months for reported frequencies of once per week or less, 2–3 times, 4–6 times, and 7 times per week or more; based on samples of 45, 212, 121, and 101 women.

quency and length of fertile period. To illustrate, assume n coitions during an intermenstrum of 25 days, with no restrictions placed on how many of the n coitions may occur in any 24 hour span. In addition, assume a rectangular fertile period of F days, present in every menstrual cycle. As before, in this hypothetical case, the monthly chance of pregnancy is

$$P(F, n) = 1 - (25 - F)^n / 25^n.$$

If $P(F, n)$ does not vary from one month to another, then, according to waiting time theory, the mean conception delay is

$$1/P(F, n),$$

while the proportion becoming pregnant in less than 6 months is

$$1 - Q(F, n)^6,$$

where $Q(F, n)$ is the complement of $P(F, n)$.

For the case where at most one coitus occurs during any 24 hours, analogous formulas may be constructed in terms of $P'(F, n)$ and $Q'(F, n)$, where

$$P'(F, n) = 1 - Q'(F, n), \text{ and}$$
$$Q'(F, n) = \binom{25 - F}{n} \Big/ \binom{25}{n}.$$

To match the conditions of Stix's sample, n is assigned successive values of 7, 11, 14 and 18 to correspond to 2, 3, 4 and 5 times per week. "F" is given values of 1, 2, and 3 to represent fertile periods of 24, 48 and 72 hours. The hypothetical mean conception delays are tabulated in the last three columns of Table 4. In these columns, the higher of each pair of values is derived on the assumption that at most one coitus occurs during any 24 hour span, while the lower value is predicated on the assumption that any number up to n coitions may occur in a 24 hour period. Immediately preceding the hypothetical delays are the empirical ones obtained by Stix and taken from Table 2. Inspection shows that the hypothetical delays are much shorter than the empirical ones, even when F is set equal to 1.

There are two reasons for this discrepancy. First, no pro-

vision is being made for unfavorable menstrual cycles. If the chance of pregnancy during a favorable cycle is p, but only "c" proportion of all menstrual cycles are favorable, then the mean pregnancy delay increases to 1/cp, larger than 1/p by a factor of 1/c. Secondly, it is being assumed that all members of a coital class share a common monthly chance of pregnancy. Actually, class members vary considerably in their fecundabilities both on account of errors in their reported coital frequency and variation in other factors influencing fecundability. It is easily shown that when two groups possess the same mean fecundability, that group which has the greater variation around this mean will exhibit the longer mean conception delay. Without knowing how variable fecundability is in each coital class, it is impossible to estimate (1-c), the proportion of unfavorable cycles, from these data. However variation in fecundability depends closely on variation in frequency of unfavorable cycles. Therefore, the fact that the hypothetical conception delays in Table 4 are so much smaller than the empirical ones, even when F is set equal to one, serves as additional evidence that the incidence of unfavorable cycles is substantial.

An identical result is obtained when hypothetical proportions conceiving in less than 6 months are calculated by means of the two models of Glass and Grebenik and compared with the empirical proportions obtained by MacLeod and Gold. Accord-

Table 4. Comparison of empirical and hypothetical mean conception delays, as related to coital frequency: Stix data.

Coital Frequency	Observed Mean Conception Delay[1]	Hypothetical Delays[2] assuming Fertile Period Length of:		
		24 Hours	48 Hours	72 Hours
	Mo.	Mo.	Mo.	Mo.
2 ×/Week	8.4	4.0	2.3	1.7
3	6.9	2.8	1.7	1.3
4	5.2	2.3	1.5	1.2
5	4.5	1.9	1.3	1.1

[1] Taken from Table 2.
[2] Calculated as $1/P(F,n)$, where $P(F,n) = 1 - (25 - F)^n/25^n$.

Coital Frequency	Observed Proportion Conceiving in 5 Months or Less[1]	Hypothetical Proportions[2] assuming Fertile Period Length of:		
		24 Hours	48 Hours	72 Hours
2	<.46	.76	.95	.989
3	<.52	.89	.99	.999
4	<.83	.94	.997	1.000
5	—	.97	.999	1.000

Table 5. Comparison of empirical and hypothetical proportions conceiving in less than six months, as related to coital frequency: MacLeod and Gold data.

[1] Because the classification of coital frequency in this table is not exactly the same as in Table 3, the values of this column must be expressed as inequalities.
[2] Calculated as $1 - Q(F,n)^3$, where $Q(F,n) = 1 - P(F,n)$ and $P(F,n)$ is defined as in Table 4.

ing to Table 5, even when F is set equal to 1, the hypothetical proportions conceiving in 5 months or less are far higher than empirical values.

What can be inferred from these data about the length of the fertile period? Obvious problems are presented by the fact that mean conception delays or proportions becoming pregnant in less than 6 months, are affected by the frequency of unfavorable cycles and by variation with respect to fecundability. However under certain conditions the *ratio* of mean conception delays of two groups may be considered as reflecting only coital frequency and length of fertile period. The necessary conditions are two. First, it must be assumed that the distribution of potential fecundabilities are the same in both groups; that is, the incidence of unfavorable cycles is the same and the distribution of monthly pregnancy chances during favorable cycles would be the same if coital frequency were identical in the two groups. Secondly it must be assumed that within a group all couples practice the same frequency of coitus and this frequency equals the one reported.[42]

[42] These assertions rest on the following argument. View fecundability as the product of two probabilities: $P_f(F,n)$, the chance of pregnancy during a favorable cycle, and f, the likelihood that the menstrual cycle will be favorable. "$P_f(F,n)$" depends on F, the length of the fertile period and n, the frequency of coitus. Let "f" be variable among couples, but constant for a given couple.

Consider two groups. In Group A, all couples have marital intercourse at a rate of n times per intermenstrum. Denote the proportion of members having an arbitrary

(Continued on page 155)

Coital Frequency	Observed Conception Delay[1]	Hypothetical Conception Delay[1] assuming Fertile Period Length of:		
		24 Hours	48 Hours	72 Hours
2 ×/Week	100	100	100	100
3	82	70	74	77
4	62	58	65	71
5	54	47	57	65

Table 6. Relative decrease of observed and hypothetical conception delays with increasing coital frequency: Stix data.

[1] The conception delays of Table 4 are restated as ratios and in each column the conception delay corresponding to a coital frequency of 2 ×/Week is taken as 100.

The mean conception delays in Table 4 are restated as ratios in Table 6. In each column the delay corresponding to a coital frequency of 2 times per week is taken as the base of 100 and the shorter delays predicated on higher coital frequencies are expressed as ratios to it. Quite obviously among the 3 sets of hypothetical ratios corresponding to fertile periods of 24, 48 and 72 hours, that one which corresponds to 48 hours comes closest to matching the empirical ratios.

This result is subject to several biases. For example, the inverse correlation between age and coital frequency may mean less subfecundity among women reporting higher rates of marital intercourse. However almost surely the largest bias comes from error in reported coital frequency. Because of this error, differences in coital frequency among coital classes are not as

frequency f_i of favorable menstrual cycles as u_i, understanding that $\Sigma u_i = 1$. Then the group's average fecundability may be represented as

$$\overline{P}_A = P_f(F,n)\,\Sigma u_i f_i,$$

and their mean conception delay as $M_A = \dfrac{1}{P_f(F,n)} \Sigma \dfrac{u_i}{f_i}$

In Group B, all couples have marital intercourse at a rate of n′ times per intermenstrum, but otherwise the conditions are those of Group A. Accordingly,

$$\overline{P}_B = P_f(F,n')\,\Sigma u_i f_i, \text{ and}$$

$$M_B = \frac{1}{P_f(F,n')} \Sigma \frac{u_i}{f_i}.$$

Hence the mean conception delays of the two groups have a ratio of

$$M_A/M_B = P_f(F,n')/P_f(F,n),$$

which depends solely on the length of the fertile period and the contrast in coital rates.

large as reported and, as a result, the above calculation tends to overestimate the length of the fertile period. Not knowing the magnitude of error, one cannot gauge the degree of overestimation. In sum, taken alone, the available data on conception delay classified by reported coital frequency support only an inference that the fertile period averages under 48 hours. However these same data have furnished additional evidence that the incidence of unfavorable menstrual cycles is high and such an incidence, combined with data reviewed earlier, suggest that the fertile period is more likely in the neighborhood of 30 hours than 18.

Summary

It is well known that only during a relatively short portion of the human menstrual cycle does coitus have an appreciable chance of leading to conception. Despite the practical importance of knowing the length of this fertile period, no general agreement has existed as to whether it averages closest to 12, 24, 36, or 48 hours.

Studies of the survivorship of sperms and ova within the female all but eliminate the possibility that the fertile period averages as long as 72 hours and even make doubtful a mean duration as long as 48 hours. However these investigations do not yield a useful indication of how much shorter than 48 hours the mean length of the fertile period may be.

Three additional estimates have been assembled. The first is taken from an analysis by Tietze who estimates the lengths of fertile period that generate reasonable conception delays given the coital frequencies reported in the female sample of Kinsey *et al.* The second and third estimates are derived by adapting Tietze's scheme of analysis to data on artificial insemination by donor and to comparisons of conception delays among women reporting different coital frequencies. Together, these three lines of evidence furnish additional reason for believing that the fertile period typically lasts less than 48 hours. However they, too, fail to settle whether the fertile period averages nearer 18 or 36 hours.

A choice between 18 or 36 hours presupposes an assumption about the combined incidence of anovulation, failure of fertilization, and early foetal wastage. If the proportion of menstrual cycles affected by these phenomena is low, then the fertile period probably averages in the neighborhood of 18 hours or a little more. If the proportion of "unfavorable" menstrual cycles reaches one half, then a fertile period nearer 36 hours must be postulated. Indirect evidence has been cited to make such a high incidence credible. However this issue is not likely to be resolved until the frequency of ova destined to abort can be estimated more confidently. Indeed, in the long run, precise estimates of the fertile period, including such aspects as "shape" and variability of length, must wait until more direct techniques of measuring the periods of sperm virility and ovum fertilizability within the female become available.

APPENDIX: AN ANALYSIS OF THREE BIASES

To apply the two models of Glass and Grebenik, Tietze has to assume that fertile periods are rectangular in shape and constant in length and that coitus is practiced at a uniform rate of n times per intermenstrum. This appendix shows that the biases associated with these simplifying assumptions are probably of secondary importance. The discussion proceeds by illustration. Attention is first given to changes in fecundability (monthly probability of conception) when a trapezoidal fertile period is substituted for a rectangular one; next when a constant fertile period is replaced by a variable one of the same mean length, and lastly when a uniform rate of coitus is replaced by variable frequencies.

A. Comparison of Trapezoidal and Rectangular Fertile Period

In keeping with Glass and Grebenik's two models, two patterns of coitus during the constant intermenstrum of 25 days are distinguished: "spaced coition" when not more than one coitus occurs during any 24 hour span; and "non-spaced coition" when any number of coituses, up to n, may occur during a 24 hour period.

In the case of unspaced coition, the shape of the fertile period does not affect fecundability. Whatever the shape of the fertile period,

chances that the ith of n cituses will not coincide with the fertile period holds constant at (25-F)/25 if F is the length of the fertile period, or, more precisely, if F is the area under the curve describing the probability that coitus will initiate pregnancy during any time point of the 25-day intermenstrum. Hence, given unspaced coition, fecundability equals $1-(25\text{-}F)^n/25^n$ for any given F and n, regardless of the shape of the fertile period.

On the other hand, if coition is spaced, shape of the fertile period does affect fecundability. Spacing intercourse increases chances that at least one coitus will coincide with the fertile period and the gain thereby derived for fecundability is maximal when the fertile period, of area F, is rectangular in shape, with height 1 and length F. The gain becomes progressively less as the shape of the fertile period changes so that its average height decreases from 1 while its base—the time interval during which chances of pregnancy are nonzero—increases from F. In the extreme, its base becomes 25 and its height uniformly F/25. Then spacing intercourse loses all significance. Whatever the patterning of n cituses, chances of not becoming pregnant remain at $(25\text{-}F)^n/25^n$.

Accordingly, if a trapezoidal fertile period is substituted for a rectangular one, fecundabilities are unaffected in the case of non-spaced coition, i.e.,

$$P(F',n) = P(F,n);$$

but in the case of spaced coition, fecundabilities are somewhat reduced, i.e.,

$$P'(F',n) \leq P'(F,n).$$

More generally,

$$P(F,n) \leq P'(F',n) \leq P'(F,n).$$

To illustrate, let the fertile period have a symmetrical trapezoidal shape such that its base equals 3; its height equals 1; and with sides sloping inward at 45 degrees, its upper parallel equals 1. These dimensions determine an area of 2, spread over a base of three unequally fertile days. Assume spaced coition so that at most one coitus coincides with the first third, the central third, or the last third of the fertile period. The probability that a single coitus coinciding with one of these three fertile days will initiate pregnancy is .5, 1.0, and .5 respectively. Hence the probability $Q'(F',n)$ of not becoming pregnant, given n spaced cituses, is the sum of four com-

Coital Frequency (per Intermenstrum)	Monthly Probability of Pregnancy (Fecundability)		
	Coition Not Spaced[1]	Coition Spaced	
		Trapezoidal Fertile Period[2]	Rectangular Fertile Period[3]
4	.28	.29	.30
8	.49	.53	.55
12	.63	.71	.74

[1] Values based on $P(2,n) = 1 - 23^n/25^n$.
[2] See text for derivation of $P'(F',n)$ values.
[3] Values based on $P'(2,n) = (25 - n)(24 - n)/(25)(24)$.

Table A-1. Comparison of fecundabilities when coition is not spaced, coition spaced and fertile period trapazoidal, coition spaced and fertile period rectangular, assuming a fertile period of length 2.

ponent probabilities:

Q_1 likelihood of not hitting any of the 3 fertile days,
Q_2 likelihood of hitting the first fertile day, but not the other two, and not initiating pregnancy,
Q_3 likelihood of hitting the third fertile day, but not the other two, and not initiating pregnancy,
Q_4 likelihood of hitting both the first and third fertile days and not initiating pregnancy.

That is,

$$Q'(F',n) = Q_1 + Q_2 + Q_3 + Q_4$$

$$= \frac{1}{\binom{25}{n}}\left\{\binom{25-3}{n} + .50\binom{25-3}{n-1} + .50\binom{25-3}{n-1} + .25\binom{25-3}{n-2}\right\}$$

Further,

$$P'(F',n) = 1 - Q'(F',n).$$

The interesting comparison is between $P(F,n)$, $P'(F',n)$ and $P'(F,n)$, where the trapezoidal fertile period F' and the rectangular fertile period F both have areas of 2. The comparison is given in Table A-1 for 3 levels of sexual activity.

B. Comparing Fertile Periods of Constant and Variable Length

Assume non-spaced coition and rectangular fertile periods. Under these conditions, a variable fertile period of mean length of F will generate a lower fecundability, other things equal, than a fertile

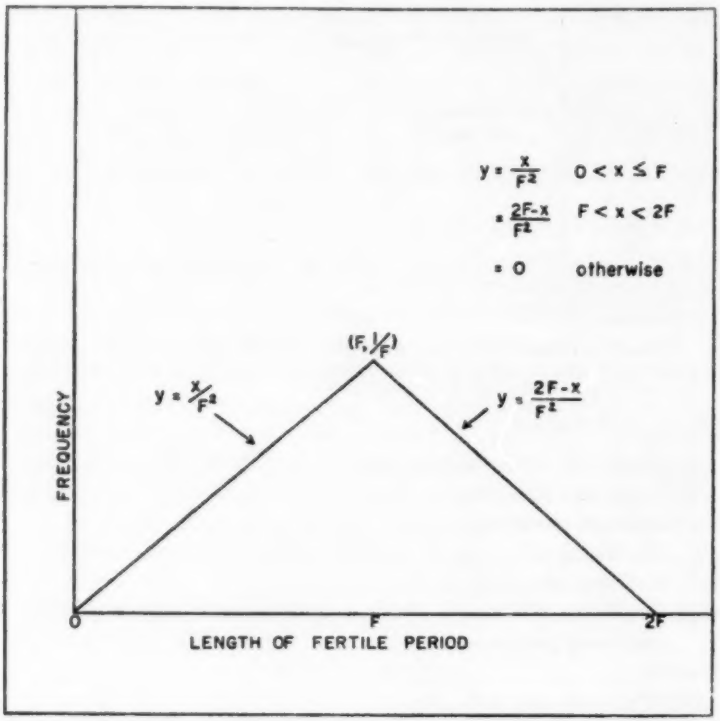

Fig. 1. Hypothetical distribution of fertile period lengths.

period of constant length F. It is desired to show that the decrement in fecundability remains small even when the variability in length is quite large.

Let x, the length of the fertile period, vary from 0 to 2F according to the symmetrically triangular density given in Chart 1. This density yields a mean length of F, a standard deviation of $(1/6)^{\frac{1}{2}}$ F, or approximately .4F, and therefore a coefficient of variation (standard deviation over mean) of approximately .4. The latter represents a substantial relative variability. Let $P(F^*, n)$ denote the fecundability associated with this variable fertile period.

$$P(F^*, n) = \int_0^F \frac{x}{F^2}\left(1 - \frac{F}{25}\right)^n dx + \int_F^{2F} \left(\frac{2F - x}{F^2}\right)\left(1 - \frac{F}{25}\right)^n dx$$

Coital Frequency (per Intermenstrum)	Mean Length of Fertile Period					
	24 Hours		48 Hours		72 Hours	
	Variable[1]	Constant[2]	Variable	Constant	Variable	Constant
4	.15	.15	.28	.28	.39	.40
8	.27	.28	.47	.49	.61	.64
12	.38	.39	.60	.63	.74	.78

[1] See text for derivation of $P(F^*,n)$ values.
[2] Values based on $P(F,n) = 1 - (25 - F)^n/25^n$.

Table A-2. Comparison of fecundabilities when fertile period constant and when variable, by coital frequency and mean length of fertile period.

By a series of algebraic manipulations, the expression on the right may be converted into a form convenient for calculation, i.e.,

$$\sum_{i=0}^{n} (-1)^i \frac{1}{(25)^i} \frac{2(2^{i+1}-1)}{(i+1)\quad(i+2)} F^i \binom{n}{i}.$$

As before, $P(F, n)$ denotes fecundability when the fertile period is rectangular and constant in length.

Table A-2 furnishes comparisons of $P(F, n)$ and $P(F^*, n)$ for several combinations of mean fertile period length and coital frequency. It is seen that the differences are generally small and diminish for shorter fertile periods and lower levels of sexual activity.

An expression is not readily available for $P'(F^*, n)$, the fecundability associating with a variable fertile period and spaced coition. As noted earlier (p. 139), the second model of Glass and Grebenik is not amenable to fractional values of F.

C. Comparison of Constant and Variable Coital Frequencies

Assume a constant rectangular fertile period and unspaced coition. Suppose further that a group is subdivided into classes representing different coital frequencies. Let w_i denote the proportion having a coital frequency of i. The group's fecundability may be represented as

$$P(F, n') = 1 - Q(F, n')$$

where

$$Q(F, n') = \Sigma w_i \left(\frac{25 - F}{25}\right)^i$$

Let $\Sigma i w_i = \overline{n}$. Then the interesting comparison will be between $P(F, n')$ and $P(F, \overline{n})$, where the latter term denotes that all members of the second group are practicing coitus at a uniform frequency of $\overline{n}$.

An analogous comparison may be constructed for the case of spaced coition. Here we have $P'(F, n)$, together with

$$P'(F, n') = 1 - Q'(F, n'),$$
$$Q'(F, n') = \Sigma w_i \binom{25 - F}{i} \Big/ \binom{25}{i}$$
$$= \Sigma w_i \frac{(25 - i)^{(F)}}{25^{(F)}} .$$

For purposes of illustration, let the sets of w_i conform to the proportionate distributions of coital frequencies reported in Kinsey's female sample for women aged 20–25 and for women aged 31–35. Respective $\overline{n}$-values are 10.34 and 9.04.

Table A-3 furnishes comparisons simultaneously between $P(F, n)$ and $P(F, n')$ and between $P'(F, n)$ and $P'(F n')$ for 3 lengths of fertile period. The differences for fecundability between stipulating distributed coital frequencies and concentration at mean frequency prove minor as compared, for example, with the differences associated with spacing or not spacing coition.

Table A-3. Comparison of fecundabilities when coital frequencies are distributed as in Kinsey's female sample or when concentrated at mean frequency, by length of fertile period.

Patterning of Intercourse	Length of Fertile Period		
	24 Hours	48 Hours	72 Hours
Distributed as among Women Aged 21–25[1]	.33–.41	.53–.61	.67–.73
Uniform Frequency of 10.34[2]	.34–.41	.58–.67	.73–.82
Distributed as among Women Aged 31–35[1]	.29–.36	.48–.55	.61–.67
Uniform Frequency of 9.04[3]	.31–.36	.53–.60	.69–.76

[1] Lower bounds based on $P(F,n') = 1 - \Sigma w_i \left(\frac{25 - F}{25}\right)^i$ and upper bounds on $P'(F,n') = 1 - \Sigma w_i(25 - i)^{(F)}/(25)^{(F)}$.

[2] Lower bounds derived from $P(F,10) + .34[P(F,11) - P(F,10)]$ and upper bounds defined analogously in terms of $P'(F,n)$.

[3] Lower bounds derived from $P(F,9) + .04[P(F,10) - P(F,9)]$ and upper bounds defined analogously in terms of $P'(F,n)$.

ANNOTATIONS

ENSURING MEDICAL CARE FOR THE AGED[1]

MR. SPIEGELMAN is a respected observer of demographic developments in the United States. His long professional association with the Metropolitan Life Insurance Company provides the base for his special insights and point of view concerning insurance approaches to protection against the economic hazards of living and of dying. His previous publications, long and short, are evidence of Mr. Speigelman's skill in drawing together and interpreting for both the professional and lay reader a wide variety of statistical reports on the facts of life and death. Mr. Spiegelman was therefore an excellent choice by the Pension Research Council for its timely study of the health needs of our growing aged population. This reviewer has been assured that publication in this election year was fortuitous. Nevertheless, the book has a special value this year and period since proposed solutions to the problems of providing and financing health services for the aged will be debated and one or more tried, following the 1960 elections. For the many alert readers who cannot hope to review the voluminous literature of the field, Mr. Spiegelman's synthesis offers much of the background for seeing and understanding reasonable approaches to paying for medical care for the aged.

One added caution seems in order. The author stresses in his preface that he has offered no proposals of his own; that "his purpose was merely to bring together the many specialized studies. . . ." He points out that "in judging a proposed solution to a social problem, it is important to consider its social

[1] Spiegelman, Mortimer: ENSURING MEDICAL CARE FOR THE AGED. Published for Pension Research Council by Richard D. Irwin, Inc., Homewood, Ill., 1960, 280 pp., 80 tables. $5.75.

consequences." That Mr. Spiegelman describes and considers the social consequences from a particular point of view is made clear particularly in the brief introductions and in the final chapter "Toward a Goal." He indicates that "the aged of the present and future have a great stake in a stabilized currency" as if this was the only conceivable solution to the maintenance of adequate purchasing power. This clue prepares the reader for the orientation toward government spending or participation in insurance programs which is implicit in the analysis of proposed solutions. Seven lines, vague in content relative to the explicit detail in other sections of the book, are devoted to the measure of the problem which would remain with an expansion of voluntary health insurance as the approach. Approximately two pages of presentation of the problems of serving the aged follow one page of description of the British National Health Service. Most of the fifteen pages reporting on the provisions of health insurance through the Old Age Survivors and Disability Insurance programs present the problems and criticisms concerning this approach.

This report is conveniently presented in seven major sections which cite close to 400 references and are illustrated with 80 tables. Background on the demographic, social, and economic characteristics of the aged is offered from a variety of sources of uneven merit, especially in the field of economics. There is a tendency to accept and interpret generously those sources which judge the aged to possess significant financial assets. One example is the author's reference to a study showing ownership of life insurance by 56 per cent of spending units at age 65 and over coupled with the hopeful judgment that "such life insurance protection can be a very significant factor in meeting the cost of terminal illness." Seven pages further on one learns that the majority of such "life insurance" is held in amounts under $2,000. The median amount for aged married couples is $1,848, for single retired males is $1,254, for single retired females is $792 and for aged widows is only $744. Two per cent or less of the aged owners of policies borrowed against them. Seventy-one per cent of aged widows owning life insurance, for example, held policies worth less than $1,000—a burial benefit for most of them, hardly to be interpreted as either financial

or psychological support in relation to the costs of even a terminal illness!

Mr. Spiegelman notes that many aged live with families. He fails however to consider the present and future economic needs of the entire family in offering the generally meager financial assets of such families as possible sources of payment for medical care for their aged members. Education, food, clothing, shelter, and even medical care in addition to T-V sets or telephones and other symbols of the American Way of Life may stand in competition for the family assets which total $500 or less for 54 per cent of all spending units according to table 2.9. Recent data from the Social Security Administration indicate that the proportion of families with whom aged parents live is greatest among the lower income groups! (FILIAL RESPONSIBILITY IN THE MODERN AMERICAN FAMILY, by Alvin Schorr, S.S.A. Dept. of H.E.W., GPO, 1960).

Mr. Spiegelman accepts an American Medical Association economist's judgment that lifetime savings are an important resource for the non-working aged person. This may be true for those with savings of significant size. Mr. Spiegelman emphasizes this aspect by pointing out that 40 per cent of spending units headed by aged persons had liquid assets of $2,000 or more. He does not state that 60 per cent have liquid assets of less than $2,000; nor that 44 per cent have liquid assets of $500 or less; nor that 27 per cent had no liquid assets. It is true that he permits the conscientious reader to see the source table from which these data were abstracted by the reviewer.

Mr. Spiegelman points out the inadequacy of uninterpreted data in his introduction and promises appropriate interpretation. In this material on the economic status of the aged there is an unfulfilled obligation to discuss its meaning in terms of patterns of illness and the need for medical care. There is always implicit the idea that all the aged person need worry about is *this* episode of illness and its costs. He is expected, Mr. Spiegelman implies on page 26, to consider as sources of payment for what is obviously his one, only, and also his last illness not only his savings but his house, his farm, and his equities in life insurance policies!

The very lucid and excellent summary of health conditions

among the aged does not appear until the next chapter. From National Health Survey data, for example the author points out that the annual incidence of acute conditions per 100 persons aged 65 and over is 155 for men and 169 for women; that the proportion of aged persons with chronic conditions is over 75 per cent with close to one-third having 3 or more chronic conditions.

Mr. Spiegelman is certainly not alone in his failure to examine the obverse face of data he presents. It is done by authors on all sides of the issues around payment for medical care. But Mr. Spiegelman has claimed objectivity. The reviewer has offered a very few of the many examples of incomplete interpretation and the failure to relate one section of the report to another in order to alert the reader of this prodigious compendium of references to some of the unconscious bias in the author's objectivity. In addition, the section on economic characteristics is marred by a technical failure—several comparisons of recent dollars are made with the dollars of earlier years without any correction for changes in purchasing power. The author calls attention to this failure at one point but, unaccountably, omits any indication of its meaning in connection with the data.

As one might expect, a more competent and less controversial discussion is offered in the brief section on health status and attitudes. There is an interesting analysis of the difference between the chances of survival from one age to another and the average lifetime or life expectancy of the population. Emphasis is given appropriately to the important role of medicine and surgery in improving the chances for survival of "impaired lives." This may account in part for the increased mortality, relative to other countries, noted in the older age groups in the United States. It also must account in part for the rise in medical care demands with age.

Mr. Spiegelman indicates the inherent difficulties in determining the health status of a population by the methods most widely used. He does not attempt to weigh the findings from the different methods nor to relate these findings to a concept of health or medical care needs. There is evidence of recognition of a cohort problem in studying both status and attitudes

(and in later chapters in relation to the demand for medical care.) However, the author does not apply this recognition of the influence of a lifetime pattern to interpretation of specific findings. Thus the author simply accepts a surveyor's analysis that there is increasing dissatisfaction with one's state of health with aging without evidence of any concern with cohort differences (p. 65)—differences related to the different world in which those now 65 and over acquired their health attitudes from the world in which those under 65 have acquired or are acquiring their attitudes.

This chapter calls for another caution to the reader. Approximately equal weight is given by the author to reports from many different studies, without comparison of the populations from which samples were drawn or any indication of the representativeness of the sample for the aged population as a whole. Clinical judgments on unidentified numbers of patients are given equal place with statistical statements concerning obviously unrepresentative samples (such as the 500 aged in the Kips Bay—Yorkville District of New York City.) Nor is there any indication of the replicability or validity of the studies reported upon. All of them, good, poor and indifferent, are credited equally by the author. Unfortunately this lack of critical judgment applies to many areas of the book.

The third section of the book reviews the medical care services of special use to the aged and the extent of utilization. Illustrated is the need for an array of services and a mechanism for bringing them to bear in a coordinated way. This point is not considered in later discussions of proposals for financing on a fragmented basis the medical services for the aged. This reviewer is also disturbed by the uncritical acceptance of the noble objectives of the currently popular graduated patient care programs and home care programs as if these objectives had been widely demonstrated achievements. No evidence is cited in the report—just editorial-like statements. Both programs are developing slowly, face many problems and they offer no assurance of quality service adapted to the patient's current needs by virtue of their mere existence as the titles of programs. The section on nursing homes gently suggests that their quality ranges "from excellent to poor" and devotes most of its

words to a description of what such homes should be like. There is no sense of the evolution of these facilities under the primary stimulus of funds from governmental sources under the Social Security Act and its amendments at the Federal level and through the welfare departments at the local level. This development under public subsidy without the exercise of quality controls is one of the clear demonstrations of a failure in the proper exercise of public responsibility for a necessary expenditure of public funds. The fact is that the level of public payment to nursing homes is tragically low and, in general, the level of care is still far from any reasonable minimum standards of qualitative adequacy.

The brief discussion of mental hospitals confuses demands for care with need since it equates waiting lists with need. A hopeful word about the role of tranquilizing drugs fails to take account of an increase in readmission rates and very great increase in the pressures on inadequate extramural mental health resources resulting from the return to the community of mentally ill patients. Little factual information is given about the availability or use of services for the care of the aged mentally ill patient.

The data on use of services are quite extensive and should provide a reasonable actuarial base for planning care as well as a baseline for observing trends under various systems of payment for care. However, there is no summary statement drawing this information together or relating it to a planning concept. One interesting point is the unexpectedly low rate of hospital utilization by aged non-white persons in terms both of discharge rates and duration of stay. Mr. Spiegelman suggests economic, geographic, educational, and cultural factors as causes. Among these might well be the simple fact that Negro physicians are more often without hospital affiliations, or have fewer affiliations, than their white colleagues. One might also consider the fact that the mortality rates for non-white persons in the oldest age group are lower than for white persons. It might be anticipated that those non-white persons who survive to ages over 65 must be in fairly good health in view of the adverse circumstances of their earlier lives.

Data on utilization and on expenditures tend to indicate

that the aged use much more medical service than do younger people with use increasing with each decade over 65. As with the younger population, the insured aged not only use more medical service but spend more cash out of pocket for such care. Furthermore the expenditures of persons over 65 appear to have increased much more than those of the population as a whole during the five years 1952–1953 to 1957–1958. In the chapter on expenditures, there is an annoying use of the term "free medical care" in several different meanings. Nowhere is it indicated that such care is always paid for by someone. One use of the term includes not only "free clinics" and professional charity but care paid for by casualty insurance, workmen's compensation, or provided in a union health facility! It is noted that O.A.S.I. beneficiaries who are also recipients of O.A.A. have higher levels of medical care utilization and expenditure. Mr. Spiegelman relates this to the larger proportion of persons aged 75 and over in the combined groups. One must add to this the fact that a large part of old age assistance is today used to pay medical costs for the medically indigent. Certainly a large proportion of O.A.S.I. beneficiaries regardless of age frequently find themselves in this category in view of their limited assets previously noted and the low levels of subsistence benefits from O.A.S.I. (averaging about $80–$90 a month). It is said that about 25 per cent of all public medical care outlays are on behalf of the aged. There is an interesting section on attitudes toward financing. The two tables report percentages giving specific responses but offer no clues as to the population base surveyed for each question. In general, attitudes reflect fairly conservative views. Relatively few persons admit to inability to find some way of paying for needed medical care. Most people think that there is some place that will take care of those who can't afford care. But there is no question about whether the respondent would like to go to such a place.

In relation to health insurance, attitude questions indicate that those who have it like it but large numbers terminate their insurance—mostly for economic reasons. Mr. Spiegelman nevertheless feels that it is an "anomaly" that 14 per cent of the aged who believe in insurance are not willing to pay for it. There is no indication of the nature of the question on govern-

ment health insurance but it is reported that "43 per cent of all aged were against it," 53 per cent of those interviewed favored it for some or all persons.

Two chapters discuss mechanisms for financing care. The emphasis throughout is on a traditional insurance philosophy. Benefit structures are described as though they were rationally related to a scientifically determined "need" for services. In fact "insurance principles" are discussed as though they were immutable law. Definitions of economic feasibility, of "unneeded" care, even of growths of plans are from the viewpoint of commercial insurance carriers. Findings in New York State in regard to extension of coverage to retiring and retired workers are declared "indicative of the developing situation." It is quietly noted that "in most instances . . . the . . . companies reduce the scale of benefits for retired employees. . . ." Standard insurance company arguments defend the high cost, low-loss ratio, and right of cancellability maintained for individual health insurance policies. Nor is there any mention of the inadequacies of the benefits in the individual policies.

Similarly, Mr. Spiegelman defends the use of the coinsurance feature to reduce premiums by deterring "unneeded use" of services. No proof is offered that coinsurance has ever accomplished this end. More recent data from the Columbia School of Public Health and Administrative Medicine Study for the Health Insurance Commissioner of New York indicate no significant difference in the use of services by matched samples of persons covered under a coinsurance feature or without it for similar benefits.

Brief but cogent pictures are drawn of public medical care programs. The equally brief summary of foreign medical care programs stresses their variety and understates the role of government. The report points out that these varied systems relate to the particular cultures of the countries concerned. Mr. Spiegelman also notes that his description has "nothing to say concerning the quality of the service. . . ." Both of these statements hold equally true for the United States.

The report concludes with the weighted outline of current proposals indicated in our second paragraph. There are adequate name and subject indices. The book is well printed on

a glare-free paper in a modern type face of adequate size for comfortable reading.

Despite our comments above, we would like to indicate that this report is a scholarly compendium of almost 400 of the most important references in the field. We have selected examples of some of the difficulties faced by the author of this unique and useful review in order to better prepare its many readers for a critical and understanding application of its contents in the formulation of a successful program for "ensuring medical care for the aged."

JONAS N. MULLER, M.D.

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NEWCOMERS: THE WEST INDIANS IN LONDON[1]

THE disturbances that took place, chiefly in Nottingham and in the Notting Hill district of London, as a result of the immigration of West Indians, shook the complacency of the English over the whole color question. It had been assumed that the English were a model of easy tolerance, ready to hold out a helping hand to in-comers of every race and creed and color. It was genuinely believed that color prejudices had been buried, when Somerset's Case and the legal decisions which followed in its wake had been absorbed into the code of conduct. In the present century the increasing communication between countries especially within what had become known and widely accepted as the Commonwealth, and the recognition given to troops from many parts of Africa who fought side by side with the British, tended to confirm this easy tolerant attitude.

When the West Indians came to England they did not settle in any special quarters, although in certain areas such as Brixton and North Kensington, there happened to be a fair concentration, but without creating what could be called a "West

[1] Glass, Ruth (assisted by Harold Pollins): NEWCOMERS: THE WEST INDIANS IN LONDON. London, Centre for Urban Studies and George Allen & Unwin, Ltd., 1960, 278 pp. 21s. (It will be published by the Harvard University Press under the title LONDON'S NEWCOMERS: THE WEST INDIAN MIGRANTS. 270 pp. $4.)

Indian Quarter." For a time it looked as if white and colored were going to settle down without notable friction. Then something happened. Matters reached a crisis with the outbreaks of anti-color violence in the summer of 1958, in Nottingham and in the Notting Hill district of London. Ordinary folk in England were angry and bewildered, and the general reaction of both press and public amounted to a strong disapproval of race discrimination. It seemed that all decent people were agreed in condemnation of prejudice and violence, although voices were raised against the indiscriminate admission of "foreigners" to Britain, mainly on the ground of housing shortage and of interfering with the prospects of employment for the British worker.

The only comprehensive information about the West Indian immigrants is the Migrant Services Division of the West Indies Commission. The Division has no funds for welfare, but it does help greatly in guiding the newcomers to social services, and in giving advice on such subjects as housing, employment, and school facilities. Since early 1954 records have been kept of all personal interviews. Nearly all the personal callers live in the London area, and in this way nearly 5,000 cards have been accumulated relating to the London position. During the past two years Ruth Glass, with the assistance of Harold Pollins, has made a careful factual analysis of this information, by the extraction of a random sample (two-ninths) of the London Group. This consisted of 1,070 persons—782 men and 288 women—and the sample may be regarded as representative of the immigrants as a whole. The study of the sample deals with a wide variety of subjects, including distribution, previous and present employment, and housing difficulties. The last creates and perpetuates the most serious problem, and it is on housing rather than industry that Mrs. Glass concentrates attention:

> As the zones of transition become more dense, their housing conditions deteriorate, their rents go up, and thus density increases even more. Most West Indians live in poor lodgings and pay high rents—both in relation to the kind of accommodation which they have, and also in relation to their incomes. Most of them can afford such rents only when they crowd together. The typical situation is that a family, or several single migrants, share one room—often a small room—in which they

> sleep, cook and eat, and spend their free time when they cannot go outdoors. The 'furniture' of the furnished room is frequently very meagre. Sanitary and washing facilities are usually shared with other tenants. It would be hard for anyone to find a *modus vivendi* in such cramped lodgings; it is hard especially for people from a milder climate, with different social habits, who have been used to being a great deal in the open air. (p. 54)

Discriminatory advertisements for housing accommodation are common enough, but not so frequent as the closed door. Schools do not offer the same difficulty, for the teachers are loyal to the public opinion of the country, which firmly rejects discrimination. Similar conditions apply, although with less force, to industry and especially to what might be called the public industries such as Transport. On the other hand there is a certain amount of occupational downgrading, due partly to the different conception of skilled work in the sending and the receiving countries, and partly on account of the awkward circumstances of promotion. There have been from time to time industrial disputes, mainly in relation to the quota of colored employees when the work situation was difficult; but on the whole the position has been manageable.

So we return to the principal difficulties, in and around the homes; and the question of attitudes has been the subject of a brilliant analysis by Mrs. Glass. This close study offers little room for complacency, because it becomes clear that the attitude of the British people is at best ambivalent: that is, a benevolent tolerance in theory, corresponding to the law and official opinion, and a cold want of understanding in the individual case. The violence which smouldered for a long time and broke out sporadically in Nottingham and Notting Dale was not, as was said hopefully at the time, the mere outburst of villainy on part of a few teddy boys and other anti-social elements. It is only too clear that the root causes penetrated more deeply than had been admitted. One of the goads to violence, to which too little attention has been given, turned out on examination to be the propaganda and action of certain illiberal groups, including the Racist groups of one kind and another—the extreme right wing and anti-colored organizations.

The penetrating study which has been so briefly outlined above ought to be widely read, because it is a fine example of the scientific approach to social issues, and also because it points clearly to the dangers of our prevalent "benevolent prejudice" towards the stranger in our land. The report gives no cause for complacency, but rather demands a closer examination of our own attitudes in Britain. The comments in the press which followed the rioting were not enough, although they helped to create a better climate of opinion; there is a sense of urgency in the summing-up made by Mrs. Glass:

> All the factors which contributed to the disturbances in Notting Dale still exist; and some have become more disturbing since. There has been neither physical nor ideological slum clearance: the housing shortage is as acute as before; fascist propaganda is more active; . . . evidence of senseless brutality is still seen each week . . .
>
> But this is not the main risk. Far more important still is the fact that, while the status of the coloured minority is an uneasy one, especially in that part of London, there are signs of further deterioration. Although the problems of the migrants are still manageable, they are cumulative." (p. 226)

JAMES M. MACKINTOSH, M.D.

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HISTORY OF FAMILY LIMITATION IN FRANCE[1]

THIS book, produced by a team of scholars associated with the *Institut national d'études démographiques* in Paris, is the first comprehensive investigation of the early history of family limitation in France. With the sole exception of the monumental MEDICAL HISTORY OF CONTRACEPTION by the late Norman E. Himes, published in 1936, it is the only such study ever made in any language. The period covered begins with

[1] Bergues, Hélène; Ariès, Philippe; Hélin, Étienne; Henry, Louis; Riquet, Michel; Sauvy, Alfred; and Sutter, Jean: *La prévention des naissances dans la famille: ses origines dans les temps modernes.* Paris: Presses Universitaires de France, 1960. pp. 400, 12 NF.

classical antiquity and ends with the dawn of the 19th century. Three-fourths of the volume is devoted to a massive documentation from contemporary sources and to their critical analysis, mainly by Mme. Bergues. The remainder consists of four interpretative essays, representing the points of view, respectively, of the cultural historian (Ariès), the Catholic theologian (Riquet), the physician (Sutter), and the demographer (Henry); and an overview from the pen of Sauvy.

In spite of the authors' scholarship and obvious industry, the findings of the inquiry are disappointing in terms of factual data and well-supported inferences. This result was probably unavoidable owing to the personal and intimate nature of the information sought.

Sauvy summarizes his conclusions as follows: (a) in the 17th century a desire to prevent births existed in a certain number of families of the aristocracy and the middle classes; (b) in the 18th century birth-control practices had become sufficiently widespread to attract the attention of writers from 1750 onwards; (c) by about 1775 the national statistics show the effect of family limitation (pages 381–382).

Little new information about the means of fertility control used in France during the *ancien régime* has come to light. Withdrawal, euphemistically referred to as "cheating nature," was almost certainly the most popular method, later supplemented by condoms and ablutions (the *bidet* appears about 1710). There is no evidence that abortion was more widely practiced in the 17th and 18th centuries than previously.

The principal factor motivating family limitation, according to Sauvy, was a growing discrepancy between rising standards of consumption and the means of gratifying the new wants, including an increasing concern for the life, health, and proper raising of children. The adoption of contraceptive practices was facilitated by the waning influence of religion upon personal conduct. This last factor may have been of particular importance in France where the religious crisis of the 16th century had not resulted in a clear victory for either the Reformation or the Counterreformation, but in a precarious equilibrium.

CHRISTOPHER TIETZE, M.D.

IMMIGRANTS IN AUSTRALIA[1]

AUSTRALIA has had a marked population growth since the last war. Its 1947 Census indicated 7.5 million inhabitants. There are now approximately 10 million. This large growth has arisen from a persistently high post-war birth rate and a large number of immigrants from Europe.

For many years prior to World War II Australia's few immigrants came mainly from the mother country. After the War, she embarked on a policy to bring more immigrants not only from England but also from other countries of Europe. She not only opened her doors to the newcomers; she instituted an expensive program of assistance for them.

True, self-interest rather than humanitarianism may have prompted and shaped Australia's post-war immigration policy. There was need for workers owing to the low level to which the birth rate had fallen during the 'thirties. Perhaps even more relevant was a gnawing fear that a half-empty continent would be tempting to crowded Asian countries.

However, even if the pro-immigration policy was prompted by concern over national survival or by the desire to keep Australia white, it doubtless required a considerable amount of courage and imagination. There were elements of world citizenship in Australia's leading rôle in the post-war assistance of migration from Europe, and in her taking well over her proportionate share of displaced persons from that continent. There were elements of religious toleration, if not boldness, in the willingness of a small and predominantly Protestant country to welcome non-Protestants among her post-war immigrants.

Australia has provided the world with an interesting experiment in assisted immigration. Within this setting it is but natural that during the past decade the Department of Demography of the Australian National University, under the leadership of Professor W. D. Borrie, has devoted much attention to studies of the new immigrants within the country.

[1] Zubrzycki, Jerzy: IMMIGRANTS IN AUSTRALIA. A Demographic Survey Based upon the 1954 Census. Melbourne, Melbourne University Press on behalf of the Australian National University, 1960, 118 pp., 57s. 6d.

————: IMMIGRANTS IN AUSTRALIA: Statistical Supplement, Canberra, The Australian University, 1960, paper bound, 108 pp. Price not indicated.

The author of IMMIGRANTS IN AUSTRALIA, Jerzy Zubrzycki, made a somewhat parallel study, POLISH IMMIGRANTS IN BRITAIN: A STUDY OF ADJUSTMENT, which was published in 1956. In the present book his purpose "is to discover the characteristic distributions of the several ethnic groups that go to make up the population of Australia." (p. ix) The five chapters are respectively concerned with (1) the effect of immigration on the age and sex distribution of the total population, (2) the ethnic and religious characteristics of the immigrants, (3) geographical distribution of the immigrants with special reference to metropolitan areas, (4) the occupational and industry status of immigrants, and (5) the rôle of immigration in the demographic development of Australia. The book contains 58 tables and 10 charts. Seventy-five additional tables, some quite detailed were published in a separate volume as a statistical supplement.

This book was published on the eve of the 1961 Census and most of the analyses perforce relate to the 1954 Census. This is somewhat unfortunate. However, the 1947–1954 comparisons indicate the patterns and the trends although precise knowledge of the present situation must await analyses of the 1961 data. During that period the population increased by 1.4 million and over half of the increase (52 per cent) was attributable to immigration.

The immigrants had a stronger impact on the age structure than on the ethnic composition of the population. Being largely young adults, they filled the gap in this segment of the native population that had been created by the low birth rates of the 'thirties.

Despite the greater importance of immigration from non-British countries of Europe during 1947–1954 than during previous years "the overall change in the ethnic composition of Australia has been less striking than many people imagine." (p. 114) Thus in 1947, 90 per cent of the population were native Australians, 7 per cent were born in the British Isles, and 3 per cent were born elsewhere. In 1954 the corresponding percentages were 86, 7, and 7.

As for residence, the immigrants resemble the natives with respect to clustering in the cities. Perhaps partly by design in

the selection of immigrants "the economic role of immigrants has been that of reserve manpower which could readily fit into occupations where labour shortages were particularly acute." (p. 115) As for ethnic variations "the Italians are concentrated in rural industries, the United Kingdom born tend to find employment in public authority and professional services, the Dutch are prominent in building and construction, while the Central and East Europeans (mainly ex-Displaced Persons) appear to be the mainstay of manufacturing industries." (p. 115)

According to Professor Borrie's foreword, this report was prepared originally only for "internal consumption" within the Department. Doubtless this helps to explain some of its deficiencies. Otherwise one might have hoped for more efforts to bring the study up to date with non-census data or even with estimates. Also, in a study of this type prepared expressly for publication one would hope to find some effort to interview some of the migrants in order to get their stories about the impact of Australia on them. A comprehensive sociological analysis would include something about the adjustment of the migrants on various social and economic fronts, the political party characteristics of the immigrants, and the general impact of the immigrants on Australia and of Australia on them.

It is hoped that following the 1961 Census this study will be brought up to date on census characteristics and that there also will be investigations of immigration in broad economic and sociological contexts.

CLYDE V. KISER